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VOLUME VI (Old Series, Vol. XI) AUGUST, 1932 NUMBER 2

ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

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Issued Monthly

Ann Arbor, Michigan

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The Relation of Lipoid Nephrosis to Nephritis*†

By E. T. Bell, M.D., *Minneapolis, Minn.*

"Nephrosis" is now generally used in a broad sense to include all forms of renal disease which are regarded as degenerative in nature, in contradistinction to "nephritis" which refers to those of inflammatory origin. However, in recent clinical literature many writers use nephrosis in a restricted sense to designate "lipoid nephrosis" only.

For many years, two forms of glomerulonephritis have been recognized:

a. The *azotemic type* is characterized in the advanced stage by nitrogen retention. Edema is present from time to time but is not a conspicuous feature except in the acute stage and during acute exacerbations. Hypertension is nearly always present in the chronic stage, but is often absent in mild acute cases. The degree of albuminuria varies at different times, but is generally greater during acute phases. An increased number of erythrocytes is commonly found in the urine, especially during acute stages. Fatal cases terminate in uremia, and the postmortem reveals small contracted kidneys in the chronic form. There is a definite inflammatory reaction which leads to occlusion of the glomerular capillaries. In subacute and chronic forms, the impermeable glomeruli gradually become hyaline and their associated tubules undergo atrophy.

b. The *hydropic or nephrotic type* is characterized by marked edema and severe albuminuria. Death is frequently due to intercurrent infections and not to uremia. At postmortem large fatty kidneys are found. This form of renal disease, formerly named chronic parenchymatous nephritis, is now called "lipoid nephrosis". A great many investigators believe that lipoid nephrosis may be separated into two distinct types, viz., pure lipoid nephrosis, and a mixed type.

(1) Pure lipoid nephrosis. By general agreement the outstanding clinical features of this disease are the presence of marked albuminuria and severe edema, and absence of hypertension, hematuria, and renal insufficiency. Lipemia and decrease of plasma proteins, especially of plasma albumin, are also considered essential parts of the clinical picture. The anatomical definition demands enlarged kidneys, with normal glomeruli, and tubules filled with lipoid droplets. It is considered a degenerative disease of the tubules.

(2) The mixed type. This form was called "nephritis with a nephrotic

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†Presented at the San Francisco Meeting of the American College of Physicians, April 4, 1932.

tendency" by Volhard and Fahr. It is also called the nephrotic type of glomerulonephritis. The disease has all the positive features of pure lipoid nephrosis but not all of its negative characteristics. Hypertension, hematuria, or impaired renal function are demonstrable in addition to the nephrotic syndrome. There are sharp differences of opinion as to the nature of this renal disease. Many writers consider it glomerulonephritis with superimposed nephrosis, or vice versa; others regard it as a form of nephrosis; and a few believe it to be a form of glomerulonephritis. The structural changes in the kidneys have not been extensively investigated. In a limited material I found non-contracted kidneys with fatty tubules, and a definite glomerular lesion. The glomerular lesion consists chiefly of thickening of the capillary basement membrane with narrowing of the capillary lumens, but there is a variable amount of endothelial proliferation.

A number of investigators attempt to make a sharp distinction between pure lipoid nephrosis and the mixed type. Some rigidly exclude from the "pure" group every case in which there is at any time during the course of the disease an elevation of blood pressure, an abnormal number of erythrocytes in the urine, or any impairment of renal function. If the onset follows an acute infection it is considered a mixed type. Other writers are more liberal and admit to the group of pure nephroses cases that show minor deviations such as a transitory hypertension, a slight impairment of function, or a slight excess of erythrocytes in the urine.

There are very few published reports which conform to the rigid definition as outlined above. The more thoroughly the patient is studied, the more frequently some minor deviation is demonstrated; yet there are a few cases which conform to the rigid definition. It is obviously inconsistent to exclude thoroughly studied cases which show minor deviations, and to include cases with incomplete data that show nothing inconsistent with pure nephrosis. In his recent review, Leiter, 1931, seems to accept as pure nephrosis cases without complete clinical study when the pathological report stated that the glomeruli were normal.

The Clinical Phenomena of Lipoid Nephrosis

Age Incidence. According to the published reports, lipoid nephrosis occurs more frequently in children than in adults, and it comprises a larger percentage of the nephritides in the former than in the latter. Clausen, 1925, observed 125 cases of nephritis in children, of which 102 were classed as hemorrhagic (glomerular) and 23 as parenchymatous (lipoid nephrosis). In general, the age distribution corresponds to that of glomerulonephritis.

Onset. The symptom that brings the patient to the physician is usually edema, but there is often a prodromal period of weakness, loss of appetite, and general malaise which precedes the onset of edema. Schwarz and Kohn, 1922, considered the absence of preceding infection an important feature of the disease. Blackfan, 1926, found an initial acute infection in only two of fourteen cases. He contrasts nephrosis with acute glomerulonephritis in this respect. Van Slyke, 1930, found

three out of nine cases in which infection seemed to play a rôle. However, other writers do not consider the absence of preceding infection a distinctive feature. Davison and Salinger, 1927, stated that the onset may be with or without a preceding infection. The initial infection is usually in the upper respiratory tract. Aldrich, 1926, found that three of seven cases of nephrosis were preceded by a cold and that colds often cause exacerbations. Lyttle and Rosenberg, 1929, found a history of infection in six out of eight patients. They consider persistent or recurrent infection the chief cause of chronicity. Apparently there is a history of preceding infection less frequently in nephrosis than in acute glomerulonephritis, but there is no sound reason for excluding a case from this group because it follows an acute infection.

Hematuria. All investigators who regard nephrosis as distinct from glomerulonephritis are agreed that no case with hematuria should be classed as pure nephrosis, although the majority would accept in this group cases with a slight increase of erythrocytes in the urine. Obviously the presence of a few erythrocytes does not exclude nephrosis, since Addis has shown that the urine of normal individuals commonly contains a few red cells. In the mixed type an increase of erythrocytes or even a gross hematuria is occasionally seen, but not as frequently as in acute glomerulonephritis. These differences with respect to hematuria indicate that the glomerular lesion of nephrosis is somewhat different from that of glomerulonephritis.

Albuminuria. Severe albuminuria is an essential feature of nephrosis. During the active periods of the disease large quantities of protein are excreted daily in the urine, but during remissions the amount becomes much less, and the urine may even become normal. The urinary protein is about 85 to 90 per cent albumin and the rest chiefly globulin (Van Slyke, Geill). As the albuminuria continues, the plasma proteins decrease. Corresponding with the greater loss of albumin in the urine there is a much greater decrease of plasma albumin than of globulin. It is highly probable that this depletion of the blood proteins is the basic disturbance in nephrosis which gives rise to the distinctive clinical features that set it apart as a special type of nephritis.

There is no doubt that the urinary proteins are derived from the plasma proteins. This is indicated by the high proportion of albumin in the urine and the corresponding decrease of plasma albumin. The plasma proteins are excreted by the kidneys.

Does this excretion take place through the tubules or through the glomeruli? In instances of severe albuminuria microscopic sections of the kidneys show the capsular spaces distended with protein, precipitated by the fixing reagent. This can hardly be interpreted as a reflux from the tubules since it is too widespread and uniform, and it is occasionally seen in the capsular space when there is none in the adjoining part of the tubule. Bieter, 1931, has shown that bichloride injections cause albuminuria in glomerular fish, but not in those with aglomerular kidneys. The evidence seems con-

vincing that protein is excreted through the glomerular capillaries.

Is the excretion due to injury of the glomerular capillaries, or to alterations in the plasma proteins themselves? Since normal kidneys excrete foreign protein readily, it is conceivable that the plasma proteins may be so altered by toxic substances that they are treated by the kidney as foreign protein. This seems to be what Epstein had in mind when he called nephrosis "albuminuric diabetes". This theory is supported by Andrews, Thomas and Welker, 1929, who consider albuminuria "a detoxicating mechanism for eliminating poisonous products of protein metabolism" and not primarily due to disease of the kidneys. They believe that the normal plasma proteins are so altered by combination with toxic substances that they behave as foreign proteins. According to this view it is not necessary to assume an injury of the glomerular capillaries.

But this theory is highly improbable. There are many forms of albuminuria which must be ascribed entirely to capillary injury. Simple passive congestion of one kidney causes albuminuria of the affected organ only. When the renal artery is clamped for from 30 to 60 minutes and then released a severe albuminuria results from the temporary ischemia. The urine from the other kidney is normal. Orthostatic and lordotic albuminuria depend upon circulatory disturbances in the kidney. In glomerulonephritis and the mixed type of lipoid nephrosis there is convincing anatomical evidence of capillary injury. In the light of all this evidence it seems unnecessary to invoke a special explanation for the albuminuria of pure lipoid nephrosis. Furthermore, Hewitt, 1929, has shown that purified plasma and urine albumin in nephrosis and nephritis exhibit a corresponding rotatory power indicating that they are identical. The evidence is fairly convincing that the albuminuria of both types of lipoid nephrosis is due to injury of the glomerular capillaries, even though one may be unwilling to accept the anatomical evidences of such injury.

The albuminuria of nephrosis is not different from that of glomerulonephritis except that it is often more severe and more frequently cyclic in character. Severe albuminuria is frequently seen in acute glomerulonephritis and in active chronic glomerulonephritis. The amount of albumin in the urine tends to decrease as the kidneys become contracted, probably because the capillary surface available for filtration decreases. The protein is decreased by the same factors that reduce the crystalloids.

Edema. Marked edema is an essential feature of nephrosis. It is a prominent initial symptom and often the most important cause of the patient's discomfort. Like albuminuria, it is intense in the active stages and slight or absent in the remissions. Edema is by no means peculiar to nephrosis. It occurs in glomerulonephritis, eclampsia, and amyloid disease of the kidneys. It is sometimes severe in acute and subacute glomerulonephritis, but is usually not prominent in the chronic stage. It tends to decrease as renal insufficiency develops, but some edema is usually present at times in the late stages. Renal disease with severe edema may be lipoid nephrosis,

acute or subacute glomerulonephritis, or amyloid disease of the kidneys. When severe renal edema is present, one may safely conclude that the kidneys are not contracted, but the exact structural changes cannot be inferred with certainty.

Epstein has shown that one of the most important causes of renal edema is the decrease of the plasma proteins, which lowers the osmotic pressure of the blood and causes an increased flow of fluid from the blood into the tissues. Edema usually occurs when the total protein falls below five per cent, or the albumin below two per cent; and it is nearly always present when the albumin falls below one per cent. The loss of plasma albumin lowers the osmotic pressure much more than the loss of a corresponding percentage of globulin, since the molecules of the former are much smaller. Edema may be produced experimentally by repeated bleeding of an animal until the plasma protein falls to a low level (Leiter, Barker and Kirk, Kumpf). There is no loss of albumin in the urine in this experiment. The kidneys remain normal.

The decrease of plasma protein is, however, not the only factor in renal edema. In acute glomerulonephritis edema develops before the plasma proteins have decreased. Also in lipoid nephrosis edema may develop or disappear while the plasma protein level remains unchanged. It is influenced by the fluid and salt intake and by intercurrent infections.

It is widely believed that renal edema is due to disease of the tubules. This is evidently the opinion of those who speak of "tubular nephritis" and "nephritis with a nephrotic tendency". It is supposed that a nephrotic element (tubular injury) is superimposed on an inflammatory glomerular lesion. But there is no evidence to support this theory. The renal disease in which tubular injury is most severe, viz., bichloride of mercury nephrosis, shows no edema at all or only a trace. In chronic glomerulonephritis, in which edema is usually not conspicuous, the tubular injury is much more extensive than it is in lipoid nephrosis. A majority of the tubules are in various stages of atrophy, and the persistent ones show the same accumulations of lipoid and hyaline granules as are seen in lipoid nephrosis. Fahr states that the tubular injury in nephrosis may proceed to necrosis of the tubule and subsequent atrophy of its glomerulus. In the preparations which I have studied, however, the only lesion which leads to destruction of a tubule is closure of the capillaries of its associated glomerulus. The functional disturbances in "tubular nephritis" are due to escape of plasma proteins through the glomeruli.

Decrease of Plasma Proteins. The loss of protein in the urine (albuminuria) soon leads to depletion of the plasma proteins. Albumin is decreased more than globulin since it is excreted in much greater quantity. Possibly the smaller albumin molecules escape through the glomerular capillaries more readily than the larger globulin molecules. When the total plasma protein is low the globulin exceeds the albumin because less globulin is excreted and because globulin is more rapidly regenerated than albumin. The relation of protein deficiency to edema has

been discussed above. It is possible that depletion of the plasma proteins is also responsible for lipemia and other systemic disturbances in lipoid nephrosis. Decrease of plasma proteins is not peculiar to pure lipoid nephrosis. It occurs also in the nephrotic type of glomerulonephritis (Fahr and Swanson, 1926, and Linder, Lundsgaard and Van Slyke, 1924) and in amyloid renal disease. The occurrence of this phenomenon in lobar pneumonia is not understood.

Lipemia. An increase of fats in the blood is usually found in lipoid nephrosis. The degree of lipemia is very variable but corresponds in a general way with the intensity of edema and albuminuria. Kumpf, 1931, produced lipemia as well as edema in rabbits by repeated bleedings—a result which suggests that depletion of the plasma proteins is a causal factor in lipemia. The greater part of the fat in the blood is neutral fat. Lipemia occurs also in glomerulonephritis when albuminuria and edema are conspicuous, but it disappears as the disease progresses toward uremia.

Hypertension. Hypertension is considered peculiar to nephritis and incompatible with pure nephrosis. When it is associated with a clinical picture otherwise typical of lipoid nephrosis, the disease is considered a mixed type of lipoid nephrosis. It is supposed that nephrosis has been superimposed on nephritis, or vice versa. Difficulties develop in the diagnosis of cases with transitory or slight elevations of blood pressure. The blood pressure may be moderately high on admission and normal thereafter, or it may first become elevated during the last few days of life. Occasionally the blood pressure remains at normal levels for several months, and then gradually becomes definitely high. Are cases of this type pure nephrosis or the mixed form? There are many borderline cases in which the distinction between pure and mixed lipoid nephrosis on the basis of blood pressure becomes somewhat arbitrary.

The elevation of blood pressure in nephritis is probably due to increased resistance to the flow of blood through the kidneys. Increased resistance may be caused by spastic or organic narrowing of the arterioles, or by obstruction of the glomerular circulation. In lipoid nephrosis with hypertension there is seldom any disease of the arterioles, but the glomerular capillaries are definitely narrowed by thickening of the basement membrane, and by endothelial increase. In a previous publication, 1929, I have described and illustrated this lesion.

Renal Insufficiency. The absence of evidence of renal insufficiency is an essential part of the concept of pure nephrosis. Even a slight nitrogen retention in the terminal stages is sufficient to exclude the case from the group of pure nephroses, according to the views of many writers. But some impairment of renal function is often demonstrable in nephrosis without hypertension if the function is studied thoroughly in the terminal stages. Van Slyke found a definite decrease of function, as measured by the urea clearance test, in eight of ten cases of "degenerative renal disease." Most of these were instances of lipoid nephrosis without hypertension. Three of his patients died typical uremic

deaths. Schreyogg, 1931, includes as "genuine nephrosis" three patients in whom the non-protein nitrogen was at times 70 to 75 mgm. per 100 c.c. of blood. If one excludes from pure nephrosis all cases with any impairment of renal function, one is more apt to exclude a case that has been studied thoroughly than one with incomplete data. A single determination of blood urea nitrogen does not establish the status of renal function.

A number of investigators report instances of typical pure nephrosis which later develop the features of glomerulonephritis, viz., nitrogen retention, uremia, hypertension. Shapiro, 1930, reported a pure nephrosis that later developed poor concentration (1007 to 1010), low phenolsulphonphthalein excretion (two per cent), and slight nitrogen retention. The blood pressure was never elevated. Contracted kidneys were found postmortem. Lyttle and Rosenberg, 1929, cite a pure nephrosis in a boy eleven years old, which within two months became typical acute glomerulonephritis with hypertension and nitrogen retention. Other instances in which the clinical picture shifted from nephrosis to nephritis are reported by Mason, 1926, and Christian, 1929. It is, therefore, well established that the clinical picture of pure lipoid nephrosis may pass over into that of typical glomerulonephritis.

Contracted Kidneys from Nephrosis. Fahr believes that nephrosis may progress into a contracted kidney. Mackay and Johnston, 1930, and Ehrich, 1930, describe a case of nephrosis of 17 years duration. There was no nitrogen retention and no hypertension, but a definite impairment of renal function was indicated by the low phenolsulphonphthalein output. Death was due to peritonitis. The kidneys were greatly enlarged (300 gm. each) and fatty, and about half of the glomeruli showed various stages of hyaline degeneration. Ehrich considers tubular degeneration the primary lesion.

Clinical Course. Nephrosis with definite hypertension or renal insufficiency, i.e., the mixed type, may progress to uremia, but death usually results from infection or some other cause before the blood metabolites have reached the uremic level. Nephrosis of pure type, or with only minor deviations from this clinical picture, rarely ends in uremia. Some cases recover after a duration of months or years. The disease is cyclic in character, periods of albuminuria and edema alternating with remissions during which the patient is greatly improved. The mortality is higher than in acute glomerulonephritis; and death is usually due to infections, the most frequent of which is pneumococcic or streptococcic peritonitis. Erysipelas is next in frequency.

The Rôle of Infection. It was stated above that many authors are unwilling to admit that pure lipoid nephrosis may have its onset following an infection, their objections being based in part at least upon the theory that the disease is not of infectious origin. The onset following an infectious process is evidently infrequent, but it can hardly be doubted that it occurs occasionally. All writers are in agreement, however, that low resistance to infection is characteristic of the disease. Colds and sore throat often cause the reappear-

ance of edema and albuminuria in a patient temporarily free from these symptoms. Peritonitis is a frequent complication not only as a terminal infection but at any time during the course of the disease (Schwarz and Kohn, 1926; Eckstein, 1926). It may persist for a long time, and the patient may survive one or more attacks. The organisms found in the ascitic fluid are usually pneumococci, but often streptococci.

Of great interest are the remarkable observations of Schwarz and Kohn, 1926, that a bacteriemia is present from time to time in nephrosis. They observed this in six out of nine patients studied. Such persistent infections as these authors describe suggest that infection may play a primary rôle in lipoid nephrosis. Since infection frequently causes a recurrence of the disease, why may it not be responsible for the first attack?

Pathological Anatomy

In both types of lipoid nephrosis the kidneys are large and yellowish, and their external surfaces are smooth. The tubules are filled with lipoid droplets There are no essential differences in the tubular lesions in the two forms of nephrosis. In nephrosis of mixed type the glomerular lesions are convincing and easily recognized. (Figures 1, 2, 3.) In sections stained with hematoxylin and eosin it is seen that the capillary walls are thick and somewhat hyaline in appearance but the increase of endothelial nuclei is not impressive. With the azo-carmine stain it is seen that the capillary walls are thickened because of a great increase in the width of the capillary basement membrane. In some instances there are a great many endothelial nuclei, but usually the increase is not prominent. When death occurs, as it usually does, before the disease has progressed to definite renal insufficiency, this is the usual microscopic picture. It differs from typical chronic glomerulonephritis in that there is little or no tubular atrophy and that the glomerular lesion is chiefly a thickening of the capillary basement membrane. However, when the disease has progressed to uremia, a great many hyaline glomeruli with atrophic tubules are seen. A study of the different stages in the formation of a hyaline glomerulus shows convincingly that the hyaline condition is brought about by a progressive thickening of the capillary basement membrane. The lesion is clearly primary in the glomerulus since it is prominent there before the tubule begins to undergo atrophy. A moderately contracted kidney may develop from the mixed type of lipoid nephrosis. It differs from the contracted kidney of typical glomerulonephritis in that the hyaline glomeruli arise chiefly from thickening of the capillary basement membrane and not from endothelial proliferation as in the latter. However, in typical glomerulonephritis some of the glomeruli are obliterated in the same way as in nephrosis.

In pure lipoid nephrosis, as well as in instances with only minor deviations from this picture, most authors describe the glomeruli as normal. This observation has been made so frequently that normal glomeruli are now generally considered as an essential feature of lipoid nephrosis, and there is a tendency on the part of some au-

thors to exclude instances with abnormal glomeruli from this group. Wohlbach and Blackfan, 1929, found slight glomerular lesions in their cases but attributed them to the associated peritonitis.

The idea that the glomeruli are entirely normal in pure nephrosis began with Fahr, 1914. However, Fahr later modified his view somewhat. In his article in the Henke-Lubarsch Handbuch, 1925, he describes and illustrates very striking glomerular lesions in a case which shows nothing inconsistent clinically with pure nephrosis. His illustrations are made from sections stained with hematoxylin and eosin, but they evidently represent hyaline thickenings of the basement membrane such as I have described, 1929. Fahr at first attributed the glomerular lesions to tubular disease, but later he stated that the glomerular lesion is primary. He insists, however, that the glomerular lesion is degenerative (glomerulonephrosis) and distinct from glomerulonephritis, and he believes that glomerulonephrosis may lead to tubular atrophy and a contracted kidney. Evidently Fahr still believes that nephrosis

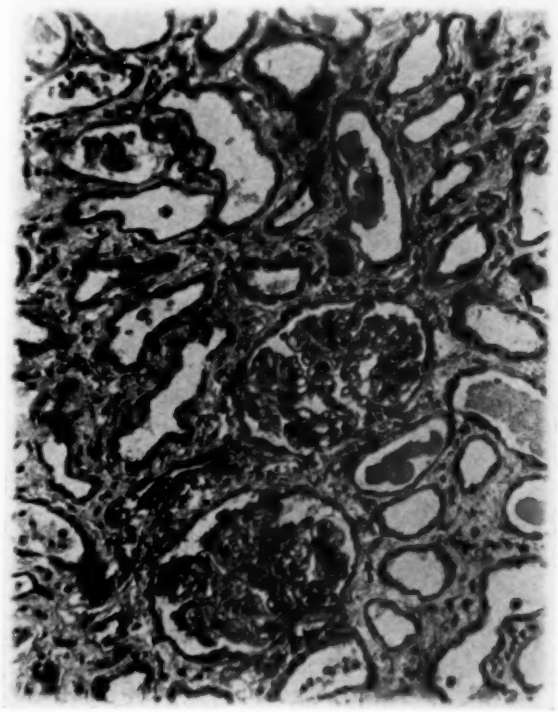

FIG. 1. Hydropic or nephrotic type of chronic glomerulonephritis. The kidneys are large and pale and the external surfaces are smooth. Note that the tubules are dilated and somewhat atrophic. The glomeruli are not enlarged and there is no increase of nuclei in them. The glomerular capillaries are very small in some lobules and completely closed in others. There are no hyaline glomeruli. Hematoxylin-eosin stain.

is a degenerative disease, but he apparently no longer maintains that the nephrotic contracted kidney results from tubular degeneration.

Aschoff, 1927, stated that there are glomerular as well as tubular lesions in lipoid nephrosis, but gives no detailed observations.

In 1929, I made a detailed histological study of the glomeruli of four cases of nephrosis which showed only minor variations from the clinical picture of pure lipoid nephrosis. These showed increase of endothelial cells or irregular thickenings of the basement membrane. It has been objected, however, that my cases were not examples of pure nephrosis. Since that time I have had the opportunity of studying three cases of nephrosis which fulfill the most rigid requirements of the pure type. Two of these cases were kindly furnished me by Dr. Klemperer of New York City. In one of these the glomeruli showed a marked irregular thickening of the basement membrane and a definite increase in the size of the endothelial cells. The lesion is more pronounced than in the four cases published by me in 1929. In Dr. Klemperer's second case there is no definite increase of endothelial cells,

FIG. 2. A single glomerulus from the preceding case. Azocarmine stain. Note the marked thickening of the capillary basement membrane. The glomerular epithelium is present in normal amount. There is no increase of endothelial nuclei. The narrowing and occlusion of the capillaries is due to thickening of the capillary basement membrane.

and the changes in the basement membrane are only slight. The third case, furnished me through the courtesy of Dr. Amberg of the Mayo Clinic, shows patchy thickenings of the capillary basement but no increase of endothelial cells.

It must be admitted, therefore, that there are instances of lipoid nephrosis in which the anatomical evidence of injury to the glomerular capillaries is only slight and perhaps not convincing. It is highly probable, however, that if the various investigators would use a stain that demonstrates the capillary basement membrane the reports of normal glomeruli would be much fewer.

Wolbach and Blackfan observed slight inflammatory changes in the glomeruli in nephrosis, but attributed them to the associated peritonitis. This interpretation cannot be disproved, yet there is evidence of disturbed glomerular function before the development of peritonitis. Also, the glomerulitis that one occasionally finds with peritonitis usually shows many polymorphonuclear and mononuclear leucocytes.

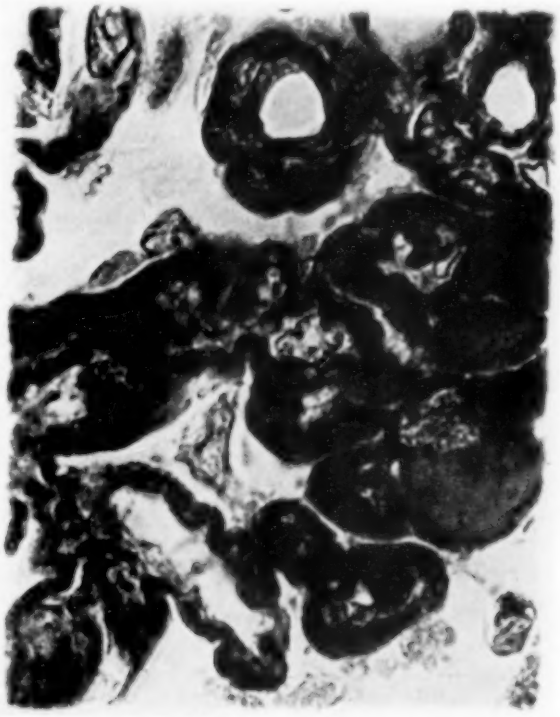

FIG. 3. Hydropic or nephrotic type of chronic glomerulonephritis. Death from uremia. There are many hyaline glomeruli with atrophic tubules. High magnification of a part of a glomerulus. Azocarmine stain. Note the extreme thickening of the capillary basement membrane with narrowing and occlusion of the capillary lumen. The thickened basement membrane shows numerous fenestrations.

Etiology and Pathogenesis of Nephrosis

(a) *Extrarenal Origin.* At the present time a majority of authors subscribe to the view that the primary cause of nephrosis is some metabolic disorder. Because of the lipemia and the fatty infiltration of the renal tubules some believe that the primary disturbance is in fat metabolism. Others, impressed by the great loss of plasma protein, believe that the basic trouble is in protein metabolism, or that it is due to toxic alterations of the plasma proteins which lead to their excretion by the kidney. The changes in the kidneys are considered secondary to the metabolic disorder; and it is contended that the renal lesion is not severe enough to produce such widespread disturbances. It is also maintained that patients with nephrosis have a very low resistance to infection and readily develop nephritis as a secondary complication.

In preceding paragraphs strong evidence has been cited, indicating that the plasma proteins are identical with the urine proteins and that they are not altered in any way. We can explain the excretion of protein only on the assumption of injury of the glomerular capillaries, even in instances where there are no histologic evidences of injury. The excessive loss of plasma protein may well be responsible for the systemic manifestations of lipoid nephrosis. It is, no doubt, largely responsible for edema; and Kumpf, 1931, has shown that repeated bleeding of a rabbit may cause lipemia.

(b) *Renal Origin.* The interpretation of lipoid nephrosis as a primary renal disease is based largely upon anatomical evidence. No other organ shows alterations of structure or function consistently. The tubules are filled with lipoid droplets, and plasma proteins escape through the glomerular capillaries. But there are two theories as to the nature of the renal lesion.

One group of authors maintains that it is a degenerative lesion affecting only the tubules. Others admit that the glomeruli may be involved, but consider the glomerular lesion degenerative in character and distinct from glomerulonephritis (Fahr). A few consider it a form of glomerulonephritis.

The theory that the disease is limited to the tubules has very little in its favor. The protein escapes from the glomeruli. The tubules are filled with lipoid droplets but they are less involved than in glomerulonephritis. When the tubules undergo atrophy it is a result of obstruction of their associated glomeruli. They do not become necrotic. It is difficult to believe that so mild a tubular injury could produce the clinical phenomena of nephrosis.

The theory that the glomerular injury is degenerative and not inflammatory in nature cannot be dismissed lightly. The chief structural change is thickening of the capillary basement membrane—a lesion that is also found in eclampsia (Bell, 1931) and in primary hypertension (McGregor, 1930). Whether this is interpreted as inflammatory or degenerative depends upon how inflammation is defined. An increase of endothelial nuclei is often found in both types of lipoid nephrosis. It is much less marked than the endothelial proliferation of typical

glomerulonephritis, but it is presumably an inflammatory reaction in both instances.

The theory that lipoid nephrosis is a distinct entity meets with great difficulties in explaining the nature of the mixed type which is generally admitted to be a form of glomerulonephritis. The advocates of this theory have no difficulty in superimposing nephrosis on nephritis, or nephritis on nephrosis. They are not in agreement as to whether nephrosis is the main disease or the appendix, although the basic conception is radically different. Volhard and Fahr considered nephritis the main disease and nephrosis the appendix, but most of their followers have reversed the sequence apparently without realizing the radical departure from Volhard and Fahr's conception.

Edema is a general feature of nephritis. There is no logical basis for the assumption that every nephritis with edema has a nephrotic component. On the other hand, it is equally difficult to believe that almost all cases of nephrosis have a nephritic component. The nephritic appendix may be a slight hematuria, a temporary hypertension, or a moderate functional impairment; or one or more of these symptoms may be pronounced. The nephrotic syndrome is too closely connected with nephritis to be an independent entity.

The theory that lipoid nephrosis is a form of glomerulonephritis is based upon both clinical and anatomical evidence. Clinically there is the gradual blending of pure nephrosis with nephrotic glomerulonephritis. If one uses delicate functional tests it is difficult to find a case without some impairment of renal function (Van Slyke). An initial clinical picture of nephrosis may pass over into that of nephritis. One is rarely certain of the diagnosis of pure nephrosis during the life of the patient. On the anatomical side, there is evidence of alterations of the walls of the glomerular capillaries in some instances of pure nephrosis and in all well-defined examples of the mixed type. The glomerular lesions are of the same type in both forms of nephrosis, but are much less pronounced in those that correspond to or approach the pure type. The lesions in the glomeruli are not identical with those of typical glomerulonephritis, since in nephrosis thickening of the basement membrane is usually more conspicuous than endothelial proliferation; but one often finds glomeruli with thick basement membranes in typical glomerulonephritis.

It is reasonable to suppose that the glomerular capillaries are first injured by some toxic substance of bacterial origin. When no reaction occurs in the capillaries, the phenomena of nephrosis develop, but when a reaction occurs (thickening of the basement membrane, endothelial proliferation) the symptoms considered characteristic of nephritis develop. When only a little reaction occurs, the patient presents slight variations from the picture of pure nephrosis. When the lesion progresses to the point of complete obstruction of the capillaries, the glomerulus becomes hyaline, its tubule undergoes atrophy, and a form of contracted kidney develops.

It is possible that the toxic substance responsible for the capillary injury is somewhat different in nephrosis and nephritis. Pneumococci seem to play a more important rôle in nephrosis.

It is widely believed that infection is not the primary cause of nephrosis since the onset is usually not preceded by an infectious process, yet there is abundant evidence that relapses are caused by infection. Randerath reported two cases in which severe infection preceded the renal symptoms, and Schwarz and Kohn have shown that bacteriemia occurs from time to time during the course of the disease. It has been shown that peritonitis may last for several months, causing a persistence of symptoms. In certain instances, at least, latent infection appears to be a primary cause of the renal symptoms and not merely a secondary factor.

Summary

Two forms of chronic glomerulonephritis are recognized: an azotemic type characterized by nitrogen retention, and an hydropic or nephrotic type characterized by marked edema and albuminuria. There are numerous transitions between these groups clinically. In the nephrotic type the kidneys are usually large and fatty, while in the azotemic type they are commonly contracted.

The hydropic type, now called lipoid nephrosis, is often subdivided into pure lipoid nephrosis and a mixed type (nephritis with a nephrotic component). The pure differs from the mixed type in the absence of hematuria, hypertension, and impaired kidney function.

When thorough and repeated studies are made, one rarely sees a case that corresponds to the rigid definition of pure nephrosis. A pure nephrosis may progress into the mixed type.

Edema is a general feature of nephritis. There is no basis for the belief that every nephritis with edema has a nephrotic component.

If nephrosis be a distinct entity, nearly all cases of nephrosis have a nephritic component.

In well-defined instances of the mixed type of lipoid nephrosis there is a marked thickening of the capillary basement membrane in the glomeruli and a variable amount of endothelial proliferation. Lesions of this type, but much less pronounced, are found in some instances of pure nephrosis as well as in nephrosis with slight variations from the pure type.

The theory is proposed that the primary disturbance in both nephrosis and nephritis is an injury of the glomerular capillaries by some toxic substance. If little or no reaction occurs in the capillaries the clinical picture of pure nephrosis develops; a moderate reaction produces some of the symptoms assigned to nephritis, viz., hematuria, hypertension, impaired kidney function; a marked reaction gives the clinical picture of nephritis.

The clinical picture depends in large measure on the character of the injury in the glomerular capillaries. When they are open and allow albumin to escape in large quantities, nephrosis develops. When they are narrowed or occluded, there is not much loss of albumin but hypertension and nitrogen ensue.

Lipoid nephrosis is not a distinct entity but a form of glomerulonephritis.

This investigation was supported by a grant from the Ella Sachs Plotz Foundation.

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The Occurrence of Cystinuria in Healthy Young Men and Women*†

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CYSTINURIA has been considered a relatively rare error of metabolism. Since the report of the first cystine calculus of the urinary tract by Wollaston in 1810, the number of observed cases has been surprisingly small. Kretschmer,[1] in a review of the occurrence of cystine calculi written in 1916, was able to find reports of only 107 cases of cystine calculi in a period of more than a century since Wollaston's original observation. The present author has reviewed elsewhere[2] the literature since 1920 and has summarized 71 cases of cystinuria, although calculus formation had not been observed in all of these.

Cystinuria in the past has usually been diagnosed by microscopic examination of the urine; the presence of the typical hexagonal plates of cystine crystals in a urinary sediment can hardly escape detection particularly if these are present in considerable numbers. The diagnosis of cystinuria has usually been made in connection with the examination of urines of patients presenting symptoms of renal colic or calculi of the genito-urinary tract. Cystinuria uncomplicated by calculus formation has been detected almost entirely by examinations of the urine of relatives of patients who have been compelled to seek surgical aid for the removal of calculi.

It seems probable that cystinuria uncomplicated by calculi may occur more frequently than is usually believed. Garrod[3] states that Simon encountered one cystine sediment in 15,000 urines examined, and Primavera, one in 20,000. Sondern[4] observed cystinuria in four urines of 35,000 specimens examined. It has been stated that only "2½ per cent of cystinurics develop stone, but the figure is probably high, on account of the large number of unrecognized cases of cystinuria".[5] Since, as already stated, cystinuria has been diagnosed almost invariably in connection with the presence of calculi, the basis of such an estimate is not clear to the present author.

In view of the interest in the familial and genetic relationships of cystinuria and in view of the paucity of data concerning the frequency of cystinuria uncomplicated by calculus formation, it has seemed of value to report the results of a systematic *chemical* examination of more than 10,000 urines of young men and women, college students for the most part, for the presence of cystine. It is hoped that the

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†Received for publication, March 26, 1932.

present report, by demonstrating the feasibility of routine chemical examination of urine for cystine, may stimulate further work by others. Only when more data concerning the incidence and genetic relationships of cystinuria are available will a more perfect understanding of this anomaly, which presents so many surgical and medical problems, be made possible.

In recent years, two chemical tests for cystine which are simple and capable of clinical application have been suggested. The first and simpler of these is the cyanide-nitroprusside test, which has been used as a test for cystine for some years, but which does not appear to have been applied to the detection of cystine in urine extensively. This test depends upon the fact that cystine may be reduced to its sulfhydryl derivative, cysteine, by sodium cyanide and that cysteine, in the presence of sodium cyanide gives a brilliant magenta color with sodium nitroprusside. Brand[6] has recently advocated the clinical use of this test in routine examination of urine, especially in cases of renal colic. We have carried out this test as follows: To 5 c.c. of urine, 2 c.c. of a 5 per cent sodium cyanide solution are added and the reaction is allowed to proceed for 10 minutes. A few drops (usually 5 drops delivered from a serological pipette of 1 or 2 c.c. capacity) of a 5 per cent solution of sodium nitroprusside are added and thorough mixing ensured. Both nitroprusside and cyanide solutions should be freshly prepared. Normal urines show a pale brown or occasionally a very faint flesh color, while with cystinuric urines a rather stable magenta color is obtained. Protein, if present in the urine, should be removed before testing; this can best be accomplished by heat coagulation and removal of the precipitate by filtration.

The color developed is similar to that obtained in the well known nitroprusside test for creatinine (Weyl) or acetone (Legal). However color production with these substances is obtained only in the presence of a stronger alkali, as sodium hydroxide. The cyanide-nitroprusside reaction is not specific for cystine or cysteine, but is given by any compound containing the sulfhydryl group (—SH) or by any compound which on reduction by cyanide is capable of yielding this sulfhydryl group.

A second *more specific* but less simply performed test is the naphthoquinonesulfonic acid test of Sullivan.[7] We have carried out this test according to the directions of Sullivan. To 5 c.c. of urine, 2 c.c. of a *freshly prepared* 5 per cent aqueous solution of sodium cyanide are added; the solution is thoroughly mixed and the reduction is allowed to proceed for 10 minutes at room temperature (20°—25°C.) One c.c of a *freshly prepared* 0.5 per cent aqueous solution of 1,2-naphthoquinone-4-sodium sulfonate* is added, the contents of the tubes are carefully mixed, and immediately 5 c.c. of a 10 per cent solution of anhydrous sodium sulfite** in 0.5 N sodium hydroxide are added. The solutions are mixed and the reaction is allowed to proceed for 30 minutes at room

*This may be obtained from the Eastman Kodak Company, Rochester, New York.

**We have found Merck's C. P. (anhydrous) sodium sulfite satisfactory.

temperature. After the addition of 1 c.c. of a 2 per cent solution of sodium hydrosulfite ($Na_2S_2O_4$) in 0.5 N. sodium hydroxide, a *pure red color* is obtained if cystine is present. With other sulfur compounds and many other biologically important substances (amino acids, carbohydrates, acetone, etc.), a yellow color is obtained. According to the extensive studies of Sullivan this reaction is more specific for cystine (or cysteine) than any of the other tests proposed.

In our experience with parallel tests in which both of these reactions were carried out, a negative cyanide-nitroprusside reaction has never been observed in a urine with which the Sullivan reaction was positive. Occasionally a weakly positive cyanide-nitroprusside reaction has been observed in a urine which showed a negative Sullivan test. We would recommend therefore that the simpler cyanide-nitroprusside test be used in routine examinations of urine for the presence of cystine, but that all urines which show a positive reaction with this test should also be tested by the reaction of Sullivan. A positive Sullivan test in the light of our present knowledge is definite evidence of the presence of cystine.

Most of the samples of urine examined were obtained in connection with the medical examinations given to entering students at the University of Michigan in the fall of 1929, 1930 and 1931. We wish to express our appreciation of the cooperation of the members of the University Health Service, Dr. W. G. Forsythe and Dr. Margaret Bell, both at the time of the fall examinations and during later follow-up examinations. Through the courtesy of Dr. Glenadine Snow and Professor Perry Brundage it was possible to examine urines of about 1100 students at the Michigan State Normal College in the fall of 1930 and with the cooperation of Professor D. L. Randall we were able to examine 106 urines collected from male students at Albion College in the fall of 1929.

The urines of a total of 10534 students have been examined (6253 men, 4281 women). We believe that the analysis of these data affords trustworthy information concerning the incidence of cystinuria in healthy individuals of the age group which includes the average student. In almost every case in which positive tests for cystine were obtained, additional samples were examined at frequent intervals. We have thus been able to study a considerable number of the group at intervals over a period of 30 months.

The results may be summarized as follows. In this series we have observed four individuals (three men and one woman) in whose urines cystine crystals have usually been present. These urines presented the typical picture of cystinuria, have given strongly positive cyanide-nitroprusside and Sullivan tests, and, as shown later in the tables, the percentage of urinary organic sulfur was distinctly higher than normal, a characteristic of cystinuria. In addition 14 individuals have been examined repeatedly in whose urines strongly positive tests by both cystine reactions were regularly obtained although cystine crystals have never been present in the urine*. We consider this group as definitely cystinuric as the first and smaller group. In none of these 18 individuals have we been

*In one individual, B. C. (Table III), cystine was isolated from the urine.

able to obtain any history of the occurrence of calculi.

The urines of a third group of 11 individuals have consistently shown weak tests for cystine by both the cyanide-nitroprusside and Sullivan reactions and in many of these urines the percentages of organic sulfur of the urine have been found to vary only slightly from the normal values. The urines of still a fourth group of 11 individuals have given occasional weakly positive color tests, particularly by the cyanide-nitroprusside reaction; but the sulfur distributions of these urines have been normal. There seems little doubt that cystinuria, in the sense of the excretion of abnormal amounts of the amino acid in the urine, may be of more common occurrence than is to be inferred from the reports of the finding of cystine calculi or cystine crystals in the urine.

In a further study of the first two groups, the distribution of urinary sulfur was determined in some instances. Under normal conditions, cystine arising from the catabolism of protein, either exogenous or endogenous, is oxidized almost completely and the sulfur present in the cystine molecule, oxidized to sulfuric acid, is excreted by the kidneys as sulfate sulfur. A small part of the total sulfur excreted in the urine is present as organic ("neutral") or unoxidized sulfur. There exists in normal urine a trace only of cystine. In the metabolic error, cystinuria, on the other hand, a very considerable part of the cystine formed in catabolism escapes oxidation and is excreted as such by the kidneys. Since the sulfur of the cystine molecule is in the unoxidized form (organic sulfur), a marked rise in the excretion of organic sulfur is observed as a characteristic of cystinuric urine.

In table I are presented studies of the distribution of the sulfur of normal urines for comparison. It will be ob-

TABLE I

PARTITION OF SULFUR IN NORMAL INDIVIDUALS

The results of analysis of all specimens not designated as 24 hour samples are calculated as grams per 100 c.c. of urine.

NAME	PERIOD	TOTAL N	TOTAL S	TOTAL SULFATE S	ORGANIC S	
	HRS.	GM.	GM.	GM.	GM.	Per cent of total S
C. A. A.	24*	12.13	0.758	0.688	0.070	9.2
L. A. S.	24	12.23	0.865	0.784	0.081	9.4
L. A. S.	24	8.24	0.677	0.605	0.072	10.6
C. E. M.	—	0.687	0.045	0.039	0.006	13.3
G. L. R.	24**	11.09	0.769	0.643	0.126	16.4
P. C. H.	—	——	0.104	0.088	0.016	15.3
B. M.	—	0.760	0.081	0.074	0.007	8.6
C. R.	—	1.36	0.136	0.116	0.020	14.7
C. W.	—	——	0.117	0.111	0.006	5.1

* Average of five consecutive 24 hour samples.

**Average of three consecutive 24 hour samples.

served that the organic sulfur comprises much less than 20 per cent of the total sulfur excreted, in most cases less than 15 per cent. In marked contrast to these values obtained for normal urines are the results of similar studies of individuals whose urine as indicated by positive Sullivan and cyanide-nitroprusside tests contained cystine (tables II and III). Values for organic sulfur as high as 40 per cent of the total sulfur excreted are commonly found and in a few individuals only does the percentage of organic sulfur fall below 20 per cent.

Particularly interesting are the results of the studies with S.P. presented in table II.* This subject was 17 years of age when first observed and has never failed to show marked cystinuria in about 25 examinations of the urine extending over a period of 18 months. Not only is the excretion of cystine very marked, but abundant cystine crystals have been present uniformly in the urine, particularly on standing. Figure 1 is a microphotograph of sediment from such a urine. This photograph was made from crystals obtained without centrifugation by means of a pipette from a urine about 30 minutes after the sample was voided. The sediment is shown to be almost pure cystine.

Despite this abundant excretion of cystine, no history of colic of the urinary tract or other indication of calculus formation has been obtained. The urine of an older brother of the patient has been examined for cystine with negative results. The analyses in the table include both 24 hour urines

*In tables II and III, unless otherwise indicated, the quantitative estimations of cystine were made by the colorimetric method of Looney.

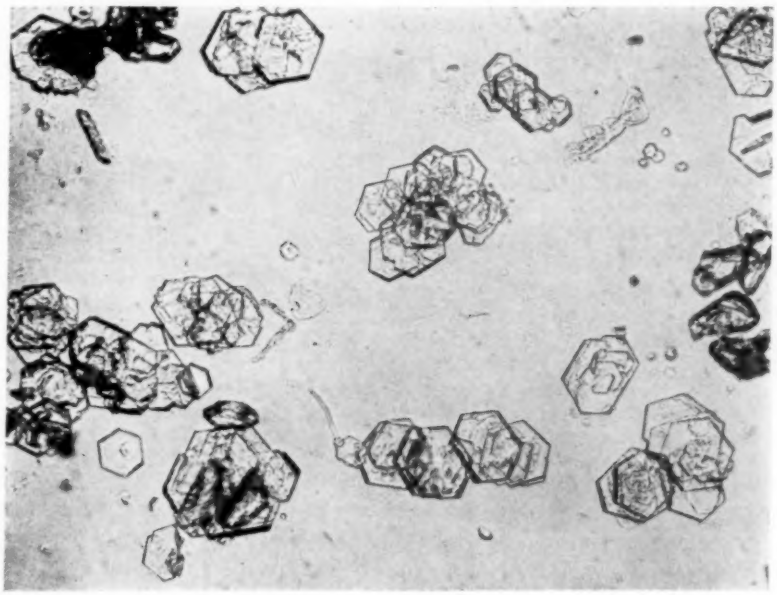

FIG. 1. Cystine crystals in the urine of subject S. P.

TABLE II
THE DISTRIBUTION OF URINARY SULFUR IN ACUTE CYSTINURIA
Subject, S. P., age 17 years

DATE	PERIOD	TOTAL N	TOTAL S	TOTAL SULFATE S	ORGANIC S		CYSTINE	SEDIMENT
	Hrs.	Gm.	Gm.	Gm.	Gm.	Per Cent of Totals	Gm.	
11- 6-30	24	11.29	0.704	0.439	0.275	39.1	0.806[1] (0.143)	Many cystine crystals
11-13-30	24	13.09	0.786	0.527	0.259	33.0	0.856 (0.176)	Many cystine crystals
11-25-30	3[2]	1.81	0.137	0.075	0.062	45.3	0.123 (0.005)	Occasional cystine crystal
1-20-31	3	1.77	0.126	0.066	0.060	47.6	0.136	No cystine crystals seen
5-1-31	24	12.60	0.774	0.481	0.293	37.9	0.920 (0.033)	Few cystine crystals
5-28-31	24	10.94	0.691	0.447	0.244	35.3	0.710 (0.214)	Many cystine crystals
12- 4-31	24	12.67	0.862	0.527	0.335	38.8	— —	Very few cystine crystals
12-15-31	3	— —	0.066	0.033	0.033	50.0	— —	Very few cystine crystals
1-11-32	3	1.62	0.120	0.062	0.058	48.3	0.156[3]	Occasional cystine crystals
1-20-32	8	3.46[4]	0.204	0.112	0.092	45.1	— —	Occasional cystine crystals

[1]Figures in parentheses indicate cystine present in sediment. This amount should be added to give the total daily cystine excretion.
[2]Urines of the three hour periods are morning urines, usually 8:45-11:45 A.M.
[3]Cystine determined by modified Okuda method.
[4]Night urine, 12:15-8:15 A.M.

and those excreted in shorter periods. The organic sulfur in urines collected over the shorter periods (three hours) appears to be higher than that of the 24 hour samples. This is undoubtedly due to the fact that much of the organic sulfur is not determined in the urines collected over the longer periods, since in these urines cystine, as shown in the tables, separates out and is not determined in the sulfur partition of the filtered urines.

Subject B.C.J. (table III) is a boy of 11 years, who has uniformly shown large numbers of cystine crystals in the urine. An elder sister of this boy was operated upon for removal of cystine calculi and was definitely cystinuric[8]. Repeated examinations of the urines of the father, mother, younger brother and four other sisters of the subject have failed to show cystinuria.

The urine of subject F.P. (table III) has always given strongly positive tests for cystine by both the Sullivan and cyanide-nitroprusside tests but in only one examination has the presence of cystine crystals in the urinary sediment been observed. This subject undoubtedly would not be recognized as a cystinuric on the basis of the usual examinations of the *urinary sediment*, but both *chemical tests* for cystine and the percentage of *urinary organic sulfur* indicate definitely a marked cystinuria. The case of H.H. (table III) is similar. In three examinations large numbers of cystine crystals were found in the urinary sediment, but the most recent examination of the urine failed to reveal cystine crystals. Despite this, the condition of cystinuria still persisted as is shown both by the intense Sullivan reaction given by the urine and by the high percentage of organic sulfur (44.1 per cent), a figure slightly higher than that previously observed in a study of this case.

The studies here reported serve to emphasize the fact that failure to detect cystine microscopically in the urinary sediment is not an adequate criterion of the absence of cystinuria. In clinical reports of cystinuria, the statement is frequently made that cystinuria is intermittent or that the cystinuria has ceased after operative removal of calculi. Reference is occasionally made to cystine calculi without cystinuria. These statements are based on the failure to detect cystine in the urine microscopically or on inadequate chemical tests for cystine. We have studied a case in which cystine calculi were removed at operation, but in which the presence of cystine crystals in the urinary sediment was detected microscopically in only one specimen of the urine.[8] However, the urines at all times showed the presence of considerable amounts of cystine on *chemical examination*. Undoubtedly this case would have been cited in the past as an illustration of the cessation of cystinuria after operative removal of calculi.

Since chemical tests, which are sufficiently simple to be adapted to clinical use, are now available for the detection of cystine, it is urged that each case of cystinuria and cystine calculus be studied carefully by the use of *chemical* methods. It is hoped that the data here presented may stimulate further study of this interesting but imperfectly understood error of metabolism. Only by carefully conducted studies can we arrive at an adequate understanding of this disturbance of metabolism.

[8]Night urine, 12:15-8:15 A.M.

TABLE III

THE PARTITION OF URINARY SULFUR IN CYSTINURIA OF "HEALTHY" INDIVIDUALS.

With the exception of the 24 hour specimens of urine all results are expressed as grams per 100 c.c. of urine.

NAME	DATE	TOTAL N	TOTAL S	TOTAL SULFATE S	ORGANIC S		CYSTINE	SULLIVAN TEST	NOTES
		Gm.	Gm.	Gm.	Gm.	Per Cent of Total S	Gm.		
F. P.	11-11-29	— —	0.167	0.093	0.074	44.3	— —	++++	Cystine isolated (Gaskell). Cystine crystals on a previous examination.
H. H.	11-18-30	— —	0.095	0.056	0.039	40.4	0.083	++++	Cystine crystals abundant.
H. H.	2- 6-32	— —	0.077	0.043	0.034	44.1	— —	+++	No cystine crystals.
B. C. J.	11-20-30	10.59*	0.613	0.425	0.188	30.7	0.605	++++	Cystine crystals abundant. Previous examination 56 mg. cystine per 100 c.c.
B. C.	11- 3-29	— —	0.097	0.066	0.031	31.9	— —	+++	Small amount of cystine isolated. (Gaskell).
B. C.	11-18-30	— —	0.057	0.044	0.013	22.8	— —	+	
B. C.	1- 8-31	0.85	0.047	0.033	0.014	29.9	— —	+	

E. L. T.	1- 7-31	0.89	0.056	0.040	0.016	28.6	— —	++	
E. L.T.	1-10-31	12.19*	0.852	0.693	0.159	18.7	— —	+	
E. L. T.	1-17-31	1.30	0.094	0.072	0.022	23.4	— —	+	
E. L. T.	11- 4-31	— —	0.084	0.065	0.019	22.6	— —	+++	
E. L. T.	1-19-32	8.90*	0.624	0.454	0.170	27.2	— —	++	
S. L.	12- 1-30	— —	0.029	0.016	0.013	44.8	— —	+	4 previous examinations showed Sullivan test ++
D. W.	10-20-30	0.737	0.047	0.037	0.010	22.9	— —	+	
D.W.	11- 5-31	— —	0.042	0.032	0.010	23.8	— —	+	
M. S. D.	1- 9-31	— —	0.050	0.039	0.011	22.0	— —	+	
C. H.	11-20-30	— —	0.138	0.113	0.025	18.1	0.046	++	
H. E.	7-12-31	7.56*	0.518	0.425	0.093	18.0	0.103	++	Frequent previous examinations over 2 yr. period Sullivan ++
L. C. W.	11- 6-31	— —	0.047	0.038	0.009	19.2	— —	++	

*24 hour specimens of urine

We wish to express our appreciation of the cooperation of the staff of assistants who have assisted in the routine examinations of so many urines in a short period of time. In particular, credit is due to William T. Krebs, Robert W. Virtue, Robert L. Grant, and Svend Pedersen for their aid in the work. Grants from the Faculty Research Fund of the University of Michigan have made it possible to carry on this work.

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Effects of the Administration of Glucose and Insulin on the Glycogen Content of Normal and Experimental Damaged Livers*†

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THE glycogen of the liver has a far reaching influence on the well-being of the body. Not only is the metabolism of carbohydrates, fats, and probably proteins disturbed when hepatic glycogen is drastically diminished, but the liver and the entire organism become more susceptible to toxic influences causing functional or organic damage. The glycogen content of the liver is reduced in diffuse injuries to this organ. This is true both of experimental animals after such procedures as administration of hepatic poisons or ligature of the common bile duct and of human beings suffering from diseases of the liver. A virtual disappearance of hepatic glycogen has been established in cases of acute yellow atrophy of the liver by Umber[1] and by Kimura.[2]

Evidence has accumulated to show that the amount of glycogen found in the liver at any given time represents the balance between continuous building up and release of this substance as glucose rather than the extent of its storage, analogous to that of fat. This new conception is shifting the emphasis from a deficiency of glycogen to the underlying disturbance in carbohydrate metabolism of which glycogen, although representing only one link, is a very useful indicator. It is interesting that in experimental injury of the liver, simultaneously with the decrease in glycogen, there is an influx of fat with increased formation of intermediary substance, e.g., ketone bodies.[3] Parallel with this goes a lowering of the blood sugar level and other disturbances of blood sugar regulation.[4]

From the point of view of clinical medicine it is important whether the faulty metabolism seen in diseases of the liver and expressed in a low hepatic glycogen can be favorably influenced by therapeutic measures. With this object oral and intravenous administration of glucose has been practiced for years, especially in cases of delayed chloroform poisoning and in acute yellow atrophy of the liver. Since the advent of insulin this hormone has been used in conjunction with glucose in many forms of hepatic disease.

Numerous reports of favorable curative or symptomatic results with the insulin-glucose therapy have emanated largely from German and French clinics regarding cases of subacute yellow atrophy of the liver, catarrhal

*Presented at the San Francisco Meeting of the American College of Physicians, April 5, 1932.

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jaundice, arsenical hepatitis, cirrhosis of the liver, lues of the liver, acute phosphorus poisoning, cholecystitis, and carcinoma of the liver.[5-14] As basis of this therapy the authors to whom reference has been made invariably mentioned an increase in the glycogen content of the liver after administration of insulin and glucose. Since in the literature there are no data on the behavior of glycogen in damaged livers, this assumption rests on an analogy with certain observations on normal animals. Only one medical writer, Ravdin,[15] on theoretical grounds advises caution regarding the use of insulin in hepatic diseases.

The Effect of Glucose and Insulin on the Glycogen of the Normal Liver

It is a mooted question whether insulin favors the deposition of hepatic glycogen in the non-diabetic animal. Depending on experimental conditions increase, no change, or decrease in the glycogen of the liver after insulin and glucose have been reported by different investigators the majority of whom performed no comparative experiments with glucose alone.

Among the authors who report such control experiments Macleod[16] found that the addition of insulin retarded the deposition of glycogen after glucose in starved animals with a low initial glycogen content of the liver. In animals with an abundance of hepatic glycogen the insulin actually reduced the glycogen of the liver in spite of the administration of glucose. Cori and Cori[17] also found less glycogen in the livers of their rats after insulin plus glucose than after glucose alone. From a complete balance sheet for ingested sugar they calculated that in the experiment without insulin three times as much of the given glucose was deposited in the form of glycogen as in the experiment with insulin.

Finally, Rubino, Varela and Collazo,[18] who studied the hepatic glycogen in a series of rabbits over a period of twenty-four hours, found that after insulin and glucose there was a sharp rise in glycogen at the two-hour period followed by a rapid decline which ended in a level below that at the beginning of the experiment. On the other hand the animals which received only glucose exhibited an increased glycogen content of the liver throughout the twenty-four hours of observation.

An explanation for such a decreased deposition of glycogen was offered by the Coris[19] who found that under the influence of insulin more carbohydrate was oxidized leaving less to be deposited as glycogen. When they increased the amount of glucose given to the insulinized animals to the point where their blood sugar was maintained on the same level as that of the animals which had received glucose alone, the same amount of glycogen was found in the livers in both groups. According to this evidence the amount of glycogen deposited in livers of normal animals is a function of the height of the blood sugar.

In our experiments rabbits were given 0.5 units of insulin plus 2.5 gm. of glucose per kgm. of body weight and sacrificed three hours later for glycogen determinations.* In normal animals there was an average increase of

*Experimental methods and protocols are given in reference 4.

hepatic glycogen from 5.8 per cent before to 8.5 per cent after the administration of insulin and glucose—a gain of 50 per cent.

In order to test the effect of insulin and glucose on rabbits with a low glycogen content of the liver, comparable to that in animals with diffuse hepatic damage, they were starved for three days prior to the experiment. The hepatic glycogen, which was thus reduced to an average of 0.7 per cent, rose three hours after insulin and glucose to 2.3 per cent—an increase of 200 per cent.

As a check on the preceding experiment the hepatic glycogen of a number of rabbits was reduced by administration of thyroxin. Each animal received subcutaneously over a period of five days a total dose of 7.7 mg. of this hormone per kgm. of body weight. These rabbits had an average of 0.65 per cent of glucose in the liver before, and 2.62 per cent after, receiving insulin and glucose—an addition of 300 per cent. A total of eighteen rabbits was used for these three experiments, the results of which are summarized in chart 1.

From data of the quoted writers and the above figures, two conclusions are justified: (1) In normal animals insulin plus glucose decreases the glycogen content of the liver when this is high, effects at least a temporary moderate increase when the glycogen is neither high nor low, and stimulates a relatively large deposition when it is low. (2) Administration of glucose in equal amounts without insulin results in a greater increase of hepatic glycogen.

The Effect of Glucose and Insulin on the Glycogen of the Damaged Liver

In order to ascertain the action of insulin plus glucose on the experimentally injured liver, glycogen determinations were performed on four groups of rabbits. Animals in the first group received a single large dose of phosphorus, sufficient to cause death in about twenty-four hours. The experiments were carried out fourteen hours after the injection of the poison when the glycogen content of the liver was still relatively high. The average hepatic glycogen in this group was 4.7 per cent before and 1.66 per cent after the administration of insulin and glucose—a loss of 65 per cent.

Rabbits in the second group were given daily small doses of phosphorus and the experiments were performed at a stage of poisoning when epinephrin ceased to produce a hyperglycemic blood sugar curve. This usually occurred after nine to twelve injections. The initial glycogen content of the liver in this group was quite low, averaging 1 per cent. Following insulin and glucose the hepatic glycogen was found to be further diminished to an average of 0.38 per cent—a reduction of 60 per cent. (Identical results were obtained in two rabbits with experimental cirrhosis of the liver due to manganese.)

In the third group the animals were given single large doses of chloroform to which about half of the animals succumbed during the first two days. The surviving rabbits were followed with the modified glucose tolerance test and the epinephrin test. The glycogen experiments were performed about ten

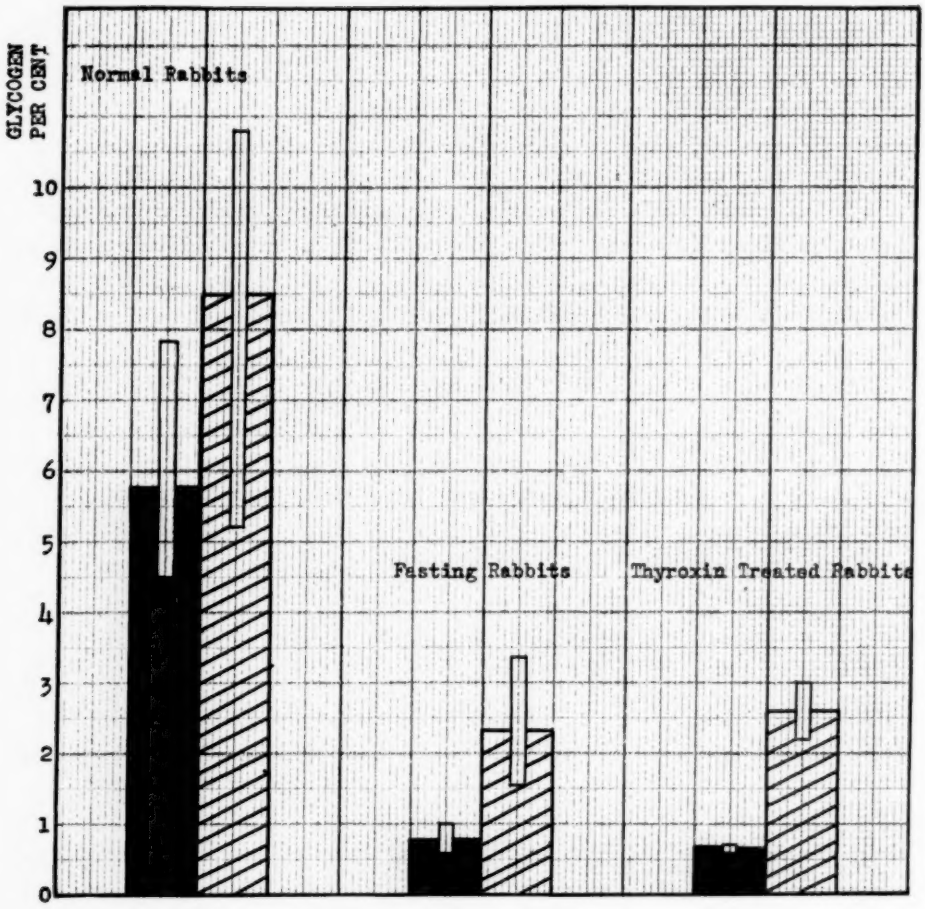

CHART 1. Glycogen content of the liver in normal, fasting, and thyroxin treated rabbits before (black columns), and after (cross-hatched columns), administration of insulin and glucose. The narrow, unshaded portion of each column shows the range of variation in each group of animals.

days following the poisoning after the hyperglycemic response to epinephrin had returned to normal and the glucose tolerance was also normal or increased, probably due to active regeneration.* The average hepatic glycogen in these rabbits was 2.3 per cent before, and 1.88 per cent after, insulin and glucose—a diminution of 18 per cent. The results of these three experiments are shown in chart 2.

In a fourth group rabbits were given small daily doses of phosphorus, and glucose alone was administered on the tenth day. Unfortunately a severe winter had caused widespread coccidiosis among rabbits in California so that most animals obtainable had a few hepatic lesions due to this infection, which appreciably lowered their resistance to toxins affecting the liver and also caused a greater variability of the

*Experimental methods and protocols are given in reference 4. Supplementary experiments with phosphorus and chloroform poisoning gave similar results.

glycogen content. Since this work will be repeated at a more favorable time it is sufficient to mention here that the average hepatic glycogen was twice as high in the rabbits which were sacrificed after having received glucose. Glycogen determinations were made in thirty-two rabbits belonging to these four groups.

The reduction of hepatic glycogen after insulin and glucose in rabbits subjected to phosphorus poisoning is unlike the already mentioned lessened deposition of this substance in the Coris' normal animals. In their case the blood sugar of the insulinized animals was lower than that of the controls. In our case the blood sugar of the poisoned rabbits due to reduced sugar tolerance was higher than that of the normal controls. As shown in a previous paper[4] the average blood sugar of six rabbits computed from blood sugar curves over three hours after administration of insulin and glucose was 126 mg. per cent before phosphorus injections were begun, and 140 mg. per cent at the stage where glycogen determinations were made.

Nor can the diminution in glycogen after insulin and glucose be explained on the bases of von Noorden and Isaac's theory of glycogen formation[20]. According to this theory glycogenesis in the liver is dependent upon the existing supply of glycogen from which energy for the polymerization of glucose is derived through its transformation into lactic acid. In our experiments we see that a relatively high hepatic glycogen in acute phosphorus poisoning fails to prevent a decrease in glycogen. On the other hand a low glycogen content of the normal liver

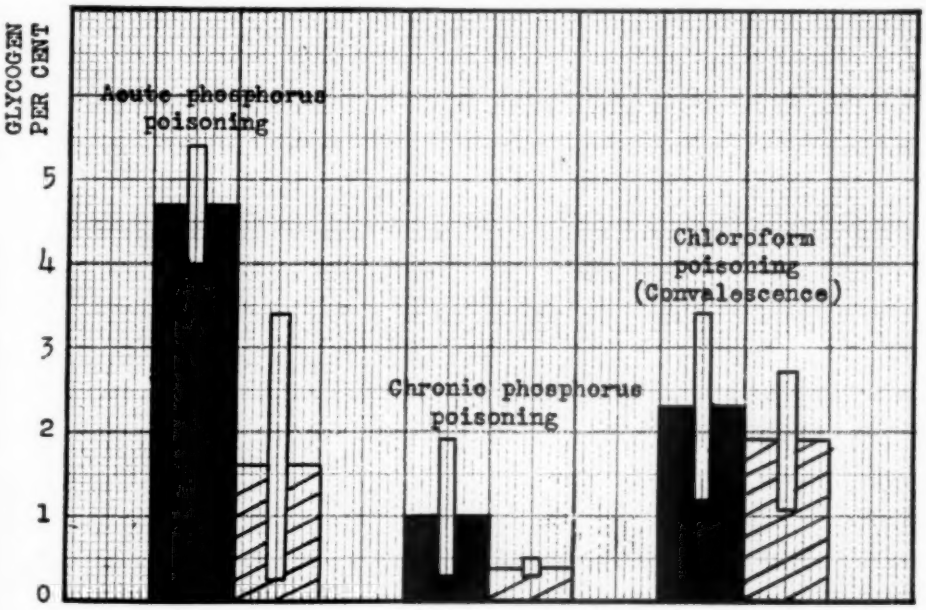

CHART 2. Glycogen content of the liver in rabbits poisoned with phosphorus and with chloroform before (black columns), and after (cross-hatched columns), administration of insulin and glucose. The narrow, unshaded portion of each column shows the range of variations in each group of animals.

does not hinder accumulation of this substance as seen from the experiments with fasting and with thyroxin medication.

The probable explanation of the decrease in glycogen of the damaged liver lies in the fact emphasized by Macleod[21] that insulin in non-diabetic animals "distorts the whole of metabolism by overstimulating certain phases of it. The excess causes some parts of the metabolic machinery to go too quickly or too slowly for other parts upon which it has no influence. Such disorganization may lead to the accumulation of intermediary products of metabolism having a detrimental influence on the working of the machine as a whole." Such a disturbance of the metabolic equilibrium would be even more marked in animals with injury of the liver. In these animals the insufficiency of hepatic parenchyma is evidently such that they fail to compensate for greater glycogenolysis due to insulin by increased glycogenogenesis in spite of an excess of glucose in the blood.

That the liver under the conditions of our experiments still retains its power of glycogenogenesis is shown by the presence of some hepatic glycogen in every examined animal. To this can be added an increase in hepatic glycogen after administration of glucose without insulin in rabbits subjected to chronic phosphorus poisoning.

In rabbits convalescing from chloroform poisoning the glycogen content of the liver was still low in spite of a practically complete structural regeneration and a normal response to the modified glucose tolerance and epinephrin tests. In addition after insulin and glucose there was a decrease in hepatic glycogen which, however, did not exceed the limits of experimental error, and therefore can be considered only as indicating that there was no rise in glycogen content. This, the last abnormality of carbohydrate metabolism to disappear during convalescence from chloroform poisoning, is explained by the work of Doljanski[22] with cultures of hepatic tissue. This author showed that active proliferation of hepatic cells in vitro is antagonistic to glycogen accumulation, but that these cells could be made to fill with glycogen by artificially slowing their growth. The same is evidently true of a rapidly regenerating liver in vivo.

The Place of Insulin in the Therapy of Hepatic Diseases

Having seen that insulin reduces the deposition of glycogen in the liver of normal animals and actually decreases the already small original amount of glycogen in the experimentally damaged liver in spite of administration of glucose, we are confronted with the question to what extent this knowledge can be applied to hepatic diseases in man. In answering this question two considerations are of importance. The first is the essentially uniform character of hepatic injury whether induced in experimental animals or spontaneously occurring in human beings. This conception, as discussed elsewhere,[23] is supported by microscopic evidence and by observations on the metabolic activity of the liver.

The second consideration is the similarity between the lesions of phosphorus and of delayed chloroform poisoning on one side, and subacute

yellow atrophy and catarrhal jaundice on the other. Incidentally it is in the last two diseases that the insulin-glucose therapy is being particularly advocated. For these reasons it is felt that the obtained data on the behavior of glycogen in experimentally injured livers have a bearing on diseases of the liver in man.

Let us turn now from the subject of hepatic glycogen to other evidence in favor of a beneficial action of insulin in diseases of the liver. Passing up such vague and unsupported statements as "stimulation of biological and fermentative processes of the liver", by insulin, we see that Blöch[3] gave concrete evidence that insulin affects derangements of lipoid metabolism. He found that administration of insulin served to lower the abnormally high level of total lipoids in the blood of patients with diffuse hepatic disease and caused a sharp drop in ketone bodies lasting for two to three hours. At the end of this period the ketone bodies, especially beta-oxybutyric acid, returned to, or exceeded, the original high level. These phenomena which Blöch associated with an assumed increase in hepatic glycogen probably are due to the opposite process of increased glycogenolysis as indicated by our glycogen determinations. Such an interpretation is also favored by this author's own observations that administration of glucose had a similar but a more prolonged effect on the lipemia and ketosis of his patients. The ultimate increase of ketone bodies after insulin would, according to this interpretation, be explained by a diminished output of glucose from the liver during the time necessary for a reaccumulation of glycogen up to the amount characteristic of the functional equilibrium of the liver in a given patient.

Whatever the explanation the significant fact is that as regards the metabolism of fats glucose accomplishes at least as much as insulin. In addition it is known from clinical observations that administration of glucose reduces prolonged coagulation time in jaundice[15] and exercises a protective action against delayed chloroform poisoning.

On the experimental side it has been shown that injections of glucose prolong the lives of animals in induced uremia and diminish the severity of lesions caused by intraperitoneal administration of trypsin, by photodynamic injury, and by a number of hepatic poisons.[24] Finally, Ravdin demonstrated increased regeneration of hepatic parenchyma due to glucose in animals with obstructive jaundice after release of the ligature of the common bile duct.

In this connection it may well be asked whether the reported beneficial effects of the insulin-glucose therapy in diseases of the liver are not accomplished by glucose and perhaps in spite of insulin. At any rate the present experimental and clinical evidence does not warrant the use of insulin in hepatic diseases unless there is a coexistent diabetes mellitus.

Summary

1. In normal animals fed glucose the injection of insulin decreases the amount of glycogen deposited in the liver. The relative increase in hepatic glycogen is inversely proportional to that at the beginning of the experiment, and in animals with a high initial glycogen content of the liver actual

diminution of this substance may result.

2. In rabbits with experimentally damaged livers the glycogen content of the liver is low. The addition of insulin to administration of glucose in these animals causes a further decrease in hepatic glycogen.

3. Insulin medication is not indicated in diseases of the liver.

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The Pituitary and the Sugar Tolerance Curve*

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THE history of the relation of a disturbance in sugar metabolism to pituitary disease may be divided into two epochs, that prior to 1911, when rough, more or less scientific observations showed glycosuria with and without the administration of sugar in one group, and the inability, in another group, to produce glycosuria after the administration of sugar; and that epoch since 1911 when Goetsch, Cushing and Jacobson showed that sugar tolerance is increased in hypopituitarism, as determined by blood sugar determinations. From that date down to the present, numerous workers have verified that observation, and in various ways have applied it to the diagnosis of hypopituitarism, in the form of the so-called sugar tolerance curve. With the advent of insulin, and the demonstration of the opposed action between the posterior pituitary hormone and insulin, further evidence of this was shown (Burn).

The introduction of the sugar tolerance curve determination heralded a means of measuring this previously noted increase or decrease in sugar tolerance, but the lack of standardization of the procedure, and other affecting measures, has led to a series of results varying from one extreme to the other. On the one hand, John said "the increase in tolerance in hypopituitarism is characteristic, almost a straight line", and Hale-White and Payne wrote that "since most definite cases of pituitary lesions tend to have an abnormal curve, the finding of a normal curve, may be considered to weigh against there being any abnormality of the pituitary functions". On the other hand, Engelbach, though having tried the application of a sugar tolerance curve determination, discontinued its use, and recently Glassberg wrote "I am unable to find any one curve which may be considered diagnostic of any of the conditions under consideration (endocrinopathies including hypopituitarism)", and further "I feel that the sugar tolerance curve as *we have used it as a routine up to this time yields no information of diagnostic value in differentiation of normal and endocrinopathic conditions.*" Such extremely divergent conclusions demand scrutiny, study and explanation.

There are a great number of factors which influence the level of the blood sugar in an individual at any given time, and these factors may vary from day to day. The coexistence of a hidden lesion or lesions, with the apparent or suspected lesion, may greatly affect the sugar level, both before and after glucose ingestion—thus disturbances of the liver, pancreas, thyroid, changes in diet, disturbed gastrointestinal function, previous starvation or "dieting," excitation, and medications. Thus "tolerance curves" repeated in a patient at an interval of even several days, may not be identical. The amount of liquids and food partaken prior to the test, excitement and

*Received for publication, Oct. 12, 1931.

pain concurrent with venous puncture (especially when repeated failures are encountered), and numerous other factors, many non-apparent and not realized, all can modify the curve, in the same individual; and although John argues that the differences in the weight of the patient and the amount of glucose taken make but little difference in the curve, and the various observers use from 25 to 100 grams of glucose, some, on a fasting status, and others on *any* previous meal, with no definite time interval, we will attempt to show that the curves will vary greatly, with the variations in the amount of glucose, fasting, or food partaken.

Thus the same patient, under identical standardized conditions, (as described later), with a different amount of glucose, after a 48 hour interval showed the following differences.

50 grams ——. 150 grams - - - -.

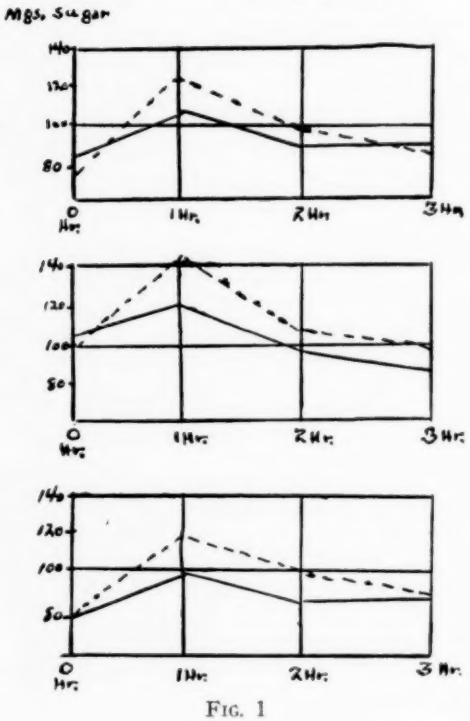

Fig. 1

Compare the curves in a case of definite hypopituitarism in a boy(Lorrain type of infantilism), given first 1.75 grams of glucose per kilogram of body weight, and again later 150 grams of glucose, one week later.

52.5 grams glucose, i.e., 1.75 grams per kgm. body weight, Body weight 30 kgm. (Curve ——). 150 grams glucose (Curve - - - -).

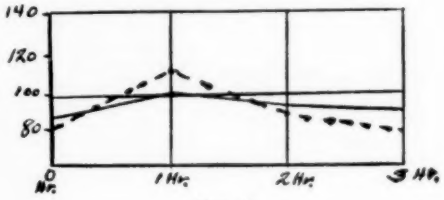

Fig. 2

The first curve (——) is that of increased tolerance, while the second curve (- - - -) is, to all intents and purposes, normal.

Note the difference below, in another case, figure 3, in the curve following a 48 hour fast (- - - -), and the non-fasting curve with the same amount of glucose, 1.75 grams per kgm. of body weight, (——), in the same patient, repeated after ten days.

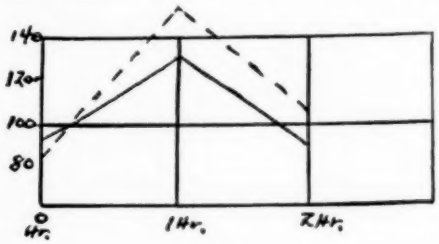

Fig. 3

Two hours before the curve (——) determination, a meal consisting of four slices of bread, dish of ice-cream,

one pastry and coffee, with two lumps sugar was given. After a study of this phase of the subject, Myers sums it up: "it is well known that the tolerance for glucose is lower in the fasting condition than after glucose has been given, apparently as a result of its stimulus to the glycogen forming mechanism, due possibly to the liberation of insulin by the pancreas. At the end of three hours this initial stimulus still appears to be sufficient to enable the normal organism to readily handle the amount of glucose given without undue hyperglycemia." The importance of the so-called standard breakfast, as later described, is thus emphasized.

Further, the blood sugar curve varies with another factor—whether so-called capillary blood (obtained by finger puncture) or venous blood is used. Note the two curves below by Foster. Foster pointed out that the blood obtained by finger puncture is virtually arterial blood. "He has found that although the sugar concentration of venous and finger (also arterial) blood is the same in the fasting state, after the ingestion of glucose there is a more rapid and greater rise in the finger blood than in venous blood." To quote Myers further, who sums up the work of Foster in this regard: "the logical explanation for this would appear to be found in glycogen formation in the muscle tissue, since the muscle stands between the arterial and venous blood. It is also apparent that when this glycogen synthesis has once been started it carries the sugar of the blood below the initial level as a result of overactivity of the glycogen forming mechanism."

Glucose curves—simultaneous venous and finger blood (Foster). Venous blood (——). Finger blood (- - - -). Amount of glucose, 100 gm.

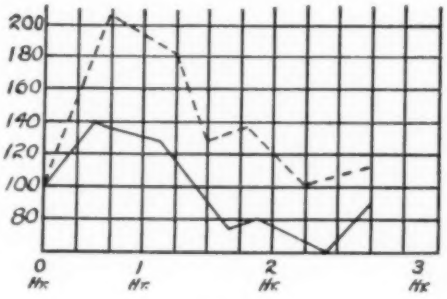

FIG. 4

In 1925 we showed that repeated injections of milk produced an increase in the sugar tolerance. Woodyatt claims that some drugs such as phosphorus and arsenic may cause glycosuria by causing an increased glycogenolysis.

Therefore, to perform the test properly, and to properly evaluate the curve produced, the effect of the administration of various diets, drugs, injections, treatments, etc., must be kept in mind. It is then apparent that discrepancies in the curves repeated in the same individuals, with the same diagnosis, can be expected, depending on:

(1) Type of blood used for the sugar determinations,
(2) Time of day the test is performed,
(3) Time of the previous meal,
(4) Nature and amount of the previous meal,
(5) Degree of pain, anxiety, excitement, and mental status of patient,
(6) Dieting and treatment of patient for the days and weeks before the test,

(7) Amount of the fluid taken with or before the glucose,

(8) Amount of glucose taken and its dilution,

(9) Presence or absence of other coexisting pathology or lesions besides the suspected condition,

(10) Individual peculiarities in rate of absorption, glycogenesis, rate of hormone manufacture, etc.

For these reasons we have followed the method of Killian, as standardized in the laboratories of the New York Post Graduate Medical School and Hospital. Without any change in diet and habits, and prior to any medication (especially thyroid, thyroxin, insulin, antuitrin, pituitrin, foreign proteins parenterally, etc.) the patient reports for his curve determination two hours after his breakfast which consisted of two slices of bread, one egg, and a cup of tea or coffee. He is first given a drink of water, the amount equal to that which will be used to make the glucose a 50 per cent solution, and he empties his bladder. One hour later, he voids again, and a specimen of venous blood is taken. He then immediately takes the glucose, 1.75 grams per kilogram of body weight in 50 per cent solution. Specimens of blood (and urine) are taken hourly for two, three and four hours. It is true that by taking only the hourly specimens the highest point may be overlooked, but for practical purposes it suffices.

Curves regarded as examples of normal tolerance.

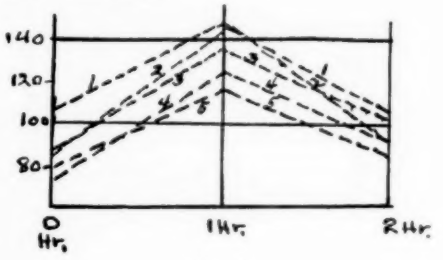

FIG. 5

From studying numerous such curves regarded as normal, we have reached the rough rule that the level at the first hour is approximately from 40 per cent to 60 per cent above the 0 hour with a tendency to return to about the 0 hour level at the end of the second hour.

We will confine ourselves at this time to more or less positive cases of hypopituitarism, without other complicating conditions, where the stigmata and clinical findings were well marked. It has been our clinical conception from some years of observation that hypopituitarism does occur without obesity (as shown in the laboratory on animals by Smith), and can also occur without much change in the sugar curve. However it is our impression that the sugar curve deviation from the normal in uncomplicated hypopituitarism is a rough measure of the degree of hypofunction.

Below are some illustrative data in a number of marked cases of hypopituitarism:

AGE	SEX	SELLA TURCICA	0 HR. BL. SUGAR	1 HR. BL. SUGAR	2 HR. BL. SUGAR
14	M	50% undersize	82	90	87
20	F	Congenitally small, clinoid processes almost completely bridged	78	80	76
18	F	50% undersize, with suprasellar shadow suggesting tumor	80	76	75
30	M	Large sella turcica, marked erosions	92	95	90

The curves in these cases approximate the flat curve, plateau or straight line described by John and others. Below are some illustrative data in a number of suspected or mild cases of hypopituitarism. We have seen a great number of such but have picked only a few to make this point clear.

AGE	SEX	SELLA TURCICA	0 HR.	1 HR.	2 HR.
25	F	1/3 undersize	92	115	101
30	F	Congenitally small	102	130	110
27	M	Negative	85	116	91
26	M	Congenitally small	96	114	93

It will be noted that here we had an elevation after glucose administration varying from 25 per cent to 37 per cent, as compared to the 40 per cent to 60 per cent rise in the normals.

The opposite syndrome—hyperfunction—may therefore give a decreased sugar tolerance, with the corresponding curve, such probably occurring in the so-called acromegalies with diabetes. These, because of treatment, x-ray or surgery, or because of a "natural burning out process" may gradually obtain an increase in their sugar tolerance, and as the original process regresses, or because of x-ray or surgery, may finally develop, as an end picture, the "flat curve" shown above, indicating, perhaps as an end picture, hypofunction.

The following case demonstrates this point. A lady, aged forty-five years gave a history of headaches of ten years duration, gradually increasing in frequency and severity, and lately noticed that her features were becoming heavier and her hands and feet larger. At this time the visual field determination showed a marked temporal constriction, and x-ray of the skull revealed a large sella turcica. Soon she began to have itching, thirst, polyuria and lost 20 pounds. Her sugar curve at this time was as follows:—

0 HR.	1ST. HR.	2ND. HR.
162	305	294

She received intensive and continued x-ray therapy. Insulin and diet seemed to be of little value, and were soon discontinued. One year later her sugar curve was as follows:—

0 HR.	1ST. HR.	2ND. HR.
93	121	107

Clinically she has gained about 30 pounds, her headaches have practically ceased, her visual fields are markedly improved, and she has become somewhat obese, lethargic and slow. With the advent of a clinical syndrome, suggesting pituitary deficiency, the sugar tolerance has swung from the extreme suggesting the diabetic curve to the other extreme, the flat curve of hypopituitarism. The reader is referred to the writings of Colwell, Allen, Lesser, and others for such similar experiences, data and impressions.

In cases of hypopituitarism (non-tumor cases with small sella turcicas, obesity, etc.), having observed a number over a period of years (fifteen such cases having been followed about eight years), we could see the changes in the sugar tolerance curve, paralleling the improvement. Below are examples of this.

		0 HR.	1ST HR.	2ND HR.
Case 1	(1923)	94	98	90
	(1926)	87	110	92
	(1930)	89	121	94
Case 2	(1925)	82	87	85
	(1928)	90	111	96
	(1930)	88	117	85

Gardner, Hill, Jones and Smith observed, too, that "with improvement the sugar tolerance curve approaches the normal".

Conclusions

From the data, observations, and literature we find the following conclusions justified:

1. Certain pituitary hormones have an action on sugar tolerance, in some respects, diametrically opposed to the action of insulin.

2. The administration of glucose to an individual will produce a curve, if the blood sugar levels following this administration are plotted.

3. The random administration of glucose—fixed amount of glucose for all patients regardless of size, fasting state, etc.—produces so variable a curve that its value in diagnosis under these conditions is nil.

4. Capillary blood curves are not identical with venous blood curves and should be discarded for curve determinations.

5. To be properly performed the method described should be followed, or some better method not yet devised.

6. When thus carried out, other things being excluded, e.g., medications, diseases, etc., deficiency is frequently characterized by an increased tolerance, the degree of tolerance increase being a rough measure of the degree of deficiency.

7. Pituitary hyperfunction is often associated with a decreased sugar tolerance resembling diabetes mellitus, but amenable in some cases to improvement, as the hyperfunction is controlled.

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Clinical Interpretation of Jaundice Based on Physiologic Principles*†

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THE tremendous value in diagnosis of bed-side approach, based on a large clinical experience is known to all. In many disease states, this suffices, and memory of characteristic symptoms, physical findings and laboratory data makes accurate diagnosis possible. The problem is not so simple in diseases associated with jaundice, a leading symptom that all may recognize easily, but which is due to so many conditions, intra- and extra-hepatic, that extreme difficulty often arises in interpretation. Here, experience alone, plus the most exact functional tests known, fails to lead to exact diagnosis in a vast number of cases. Notwithstanding painstaking reasoning and analysis, one must often admit doubt at the bedside, and defeat in the operating room or at the autopsy table. The difficulties presented prompt an attempt to create further clinical order, building upon a foundation of underlying physiologic and pathologic principles.

Jaundice is a leading objective symptom, a staining of the plasma and of the tissues, consequent upon increase in the bilirubin content, at the site of discoloration, local or general. The tissues of the body, however, do not stain equally, some actually remaining free of pigment, no matter what the intensity of general coloration. Most highly colored are the blood vessels and heart valves, the skin, mucous and serous membranes, kidneys, lungs, spleen and liver. Cartilage, the cornea, and the cerebrospinal system (brain and spinal cord) retain their normal appearance. (A single exception here is the staining of the infundibulum cerebri in some cases of icterus neonatorum gravis.) It is also interesting to note that pure secretions, exemplified by the salivary and gastric juices, and the cerebrospinal fluid, are free of bilirubin. Excretions, as urine and perspiration, are, however, deeply stained.

Numerous attempts have been made to explain this inequality of tissue staining. The facts certainly oppose acceptance of the "imbibition" theory, with its claim for general tissue absorption of the bile pigments from the circulating fluids. If this mechanism was operative, one should expect an equal staining throughout. Rosenthal[1] has attempted to answer this question. His experimental work indicates the importance of elastin, the essential substance of elastic tissue, as a fundamental

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†Received for publication, October 18, 1931.

chemical substance, attracting bilirubin. Those tissues rich in elastin stain deeply; those without elastin are free of pigment. Adipose tissue containing no elastic tissue appears intensely colored, only because of the small amount of pigment needed to contrast with the pure white of the fat. This color, too, can be washed off easily, which is not true of the other tissues. Elastin, in vitro, added to non-stainable tissues appeared to alter the response to the pigment. This chemical affinity conception also fails of complete satisfaction. It seems likely to us that the staining of a specific tissue is related also to the function of that particular tissue as regards bilirubin pigment — formative and excretory. It is most concentrated at sites of its formation in the reticulo-endothelial system (vide below), principally spleen, liver and bone-marrow, and also marked in organs of its normal and abnormal excretion— kidney, skin and intestines.

Here, one must pause momentarily to inspect the evidence concerning the nature, formation and excretion of bilirubin and its associated pigments.

Virchow[2] found crystals in extravasated blood, strongly resembling bilirubin. Knowing that they came from the hemoglobin of the red cell, though unable to furnish chemical proof of their identity, he named the substance hematoidin. The proof that this substance was bilirubin subsequently was furnished by Jaffé, Fischer, and Bumstead and Rich. The possibility has been suggested that bilirubin also may be formed from pigments other than blood hemoglobin. Myohemoglobin may contribute very slightly (Whipple, Hooper and Robscheit-Robbins). The importance of chlorophyl,[1] and its associated pigments is denied (Bollman, Sheard and Mann.) The only justifiable conclusion seems to involve blood hemoglobin as practically the sole source of supply for bilirubin formation.

Prior to Virchow, the conception prevailed that the production of bilirubin occurred exclusively in the epithelial cells of the liver. The great pathologist's finding was the first bit of evidence indicating the possibility of extra-hepatic formation. However, it did not attract its deserved attention for many years. The work of Minkowski and Naunyn[3] (1886) also appeared to corroborate the longstanding belief. Their inability to produce jaundice in hepatectomized geese with hemolytic agents, as arseniureted hydrogen, led them to the dictum "without liver, no jaundice". Several years later (1889) Löwitt,[4] producing hemolysis in the blood of frogs, found red cell debris, hemoglobin, bile pigment and an iron residue, in the Kupffer cells of the liver. He indicated that bile pigment could be formed outside the liver epithelial cell, but did not deny the latter's activity in this regard. In 1912, McNee,[5] in the laboratory of Aschoff, repeated the experiments of Minkowski and Naunyn with identical results, but now, with a new interpretation. He ascribed the absence of jaundice to the absence of the Kupffer stellate cells, so large a portion of the reticulo-endothelial system in geese. The conception of this system had been formulated recently by the Aschoff school and McNee was first to attract attention to it in connection with bilirubin formation. The other

members of the reticulo-endothelial system are the cells lining the sinuses of the spleen, the endothelium of the lymph and blood vessels, the capillaries of the bone-marrow, the serosae, the endothelium of the suprarenals, omentum, lungs, hypophysis and the macrophages of the blood.

Credit goes to Whipple and Hooper[6] for stimulating the important researches which yielded the conclusive evidence. Their deductions, however, derived from producing jaundice in animals whose livers supposedly were excluded from the circulation, were challenged. Rich,[7] Makino[8] and others denied that the liver had been excluded completely enough. Mann[9] and his coworkers, in their series of ingenious experiments, then successfully dehepatized dogs and were able to produce an icteric state with hemolytic substances. Immediate universal confirmation followed. Rich succeeded in producing jaundice following complete abdominal evisceration. The contrary findings of Rosenthal, Melchior and Licht,[10] of the Minkowski school, who failed to produce jaundice in hepatectomized dogs, after injecting such substances as toluylenediamine, were largely vitiated by such work as that of Joannovics and Pick.[11] The latter's experiments indicated that the substances used were toxic to the liver cell, and thus could not produce icterus in the absence of the liver. A mechanism therefore appeared to exist, outside the liver, which could assume the function of bilirubin formation.

Much evidence points toward the cells of the reticulo-endothelial system as active in this extra-hepatic formation of bilirubin. Kodama, [12] in experimental icterus, showed bile pigment in the Kupffer stellate cells before it could be found in the epithelial cells of the liver, and before it reached the serum. In mechanical icterus, the Kupffer cells contained much more of the pigment. Haldemann [13] demonstrated marked deposition of pigment in the reticulo-endothelial cells of the bonemarrow, after injecting laked blood intravenously. Several groups (Mann;[9] Ernst and Szappanyos;[14] Komari and Iwao[15]) demonstrated increased formation of bilirubin in the spleen and bone-marrow after injecting hemoglobin into the blood flowing to these sites, and in the perfused spleen. Lepehne,[16] and Eppinger[17] believed their attempts at blocking the reticulo-endothelial system with substances such as collargol resulted in the diminished activity in this process of bile pigment formation. Rich,[7] in tissue culture studies, noted that only mesodermal cells were able to transform hemoglobin into bilirubin, and this intracellularly, possibly with the aid of an hydrolytic ferment.

Evidence certainly indicates that the cells of the reticulo-endothelial system are able to manufacture bile pigment, under the abnormal conditions of the various experiments performed. Whether this is the only method adopted by the body in health, and what proportion of the work is performed by the various members are questions still to be answered. It is unlikely, as Mann first indicated, that the reticulo-endothelial elements of the spleen and bonemarrow are exclusively concerned in the exercise of this function. These deductions, based on work with dehepatized animals, did not seem

transferable to the intact animal, with its liver and Kupffer cells in situ. His more recent work indicates that in the absence of liver and spleen, the rate of production remains normal, presumably due to bonemarrow activity. Certainly, the ability of reticulo-endothelial cells everywhere to form bilirubin is attested by numerous clinical instances —regional icterus (Umber and Rosenberg), jaundice associated with pulmonary infarction, that following intra-peritoneal hemorrhage, etc. From analysis of the evidence presented, the reticulo-endothelial cells of the liver, spleen and bone-marrow appear to be the normal agents for bilirubin production, with the remainder of the system also capable of so functioning under more abnormal conditions.

The following facts, however, seem established with a high degree of assurance. (1) That bilirubin is formed practically entirely from the hemoglobin of broken-down red blood cells; (2) that the cellular elements of the reticulo-endothelial system are probably active in this transformation; and (3) that the epithelial cells of the liver merely excrete the pigment into the biliary radicles which convey it to the gallbladder and intestines. It is evident, therefore, that alterations in the bilirubin content of the serum, and thus the tissues, may result from single or multiple derangements anywhere along this chain of bilirubin formation and excretion. Jaundice or the state of increased bilirubin concentration therefore may be due to (1) an increased destruction of red blood cells, and overactivity of the reticulo-endothelial system (2) disease of the hepatic epithelial cells, and consequent incomplete or absolute failure of removal of bilirubin from the blood, and incomplete propulsion into the biliary radicles, and (3) blockage of the excretory channels after proper elimination by the hepatic cell.

Rich has contended recently that jaundice rarely, if ever, results from simple overproduction of bilirubin. It is his belief that the reserve power of the normal liver is so great that the organ can care adequately for any excess of bilirubin and invariably prevent the establishment of an icteric state. Disturbance of liver cell function is claimed always to co-exist. He ascribes great importance to atrophic changes in the epithelial cells about the efferent vein of the liver lobule, found in various anemic and infectious diseases. Experimentally, similar lesions have been produced, under conditions pointing toward anoxemia as the responsible factor. Although this work is highly informing and leading, it is questioned whether the facts presented warrant the entire clinical conclusion. It would seem that Rich is ascribing too great an importance to pathology, usually minor. It is likely that in chronic cases of "hemolytic" icterus that have persisted for an extended period, the degree of liver dysfunction may proceed to clinical significance. The usual case, with hemolysis of red cells the crux of the clinical picture, does not appear to require such preceding damage. Although it is true that jaundice of any marked intensity practically always has an hepatic element, icteric states of milder degree, though with definite hyperbilirubinemia and tissue staining, appear to result independent of such affection. The

increased production of bilirubin on red cell destruction may be conceived as an actual compensatory mechanism, a pigment being formed from the liberated hemoglobin which is tolerated well by the tissues, and a colorless iron-containing compound being split off which can be stored and utilized again.

It is upon the foregoing facts that our modern classifications of icterus are based. McNee[18] called the first group, "hemolytic"; the second class, "hepatocellular" or "toxic" and the third "obstructive." Although it is true that all three terms do not possess identical connotations (hemolytic and obstructive, pathogenesis; and toxic, etiologic) this grouping is simple, satisfactory, and adequate for clinical usage.

Recently, Stuber[19] suggested changes in nomenclature, attempting to add to the functional descriptiveness of the terms previously employed. He referred to the hemolytic as the "superfunction" group, since here mere over-production of bilirubin leads to its increase in the serum and tissues. Whether "superfunction" better typifies this group than "hemolytic" is questionable. The implication of blood destruction certainly is better given by the latter term, though "superfunction" is of value in indicating the overactivity of the reticulo-endothelial system. Where there is no evidence of actual hemolysis, as after hemorrhages (intraperitoneal, pulmonary), blood dyscrasias and reticulo-endotheliosis, the latter term would seem more desirable. The "hepato-cellular" group to Stuber is known as the "retention type of icterus, since even the normal quantity of bilirubin produced is partially retained, the malfunctioning epithelial cell being unable to excrete it completely. The obstructive class is called the "resorption" group. Here, no overproduction of bilirubin is found, the liver cell can propel completely the pigment brought to it, but somewhere along the course of the bile ducts, obstruction is met, and damming back of bile takes place. The continuity of the bile canaliculi is destroyed, bile reaches the perivascular spaces and is resorbed into the blood capillaries.

Rich used similar terms in his suggested classification, though with somewhat different application. "Retention" was used for cases with indirect Van den Bergh reaction and acholuria, though with increase of urobilin in urine and feces. This group includes the various forms of "hemolytic" icterus and jaundice resulting from mild interference with functions of the epithelial cells of the liver—as by anoxemia. "Regurgitation" was applied to those cases with direct Van den Bergh reactions, bile in the urine, and little or no urobilin in the stools. This class contains the forms associated with necrosis of liver cells. This classification does not appear to attach sufficient importance to clinical symptoms, nor does it adequately segregate cases on the basis of their underlying causes. Thus jaundice due to acute yellow atrophy is so essentially different clinically from that following a common duct obstruction by calculus that co-grouping is undesirable. The basis of division, i.e., using the Van den Bergh reaction, is also undesirable, since similar findings may exist in either group at some stage of the disease process.

It is important to appreciate that all the classifications in use are not rigid

and with sharp or absolute boundaries. This follows because the diseases causing jaundice are not static; they are dynamic and may regress, or, what concerns us more, may show progress. A case belonging to one group becomes modified, as a result of active etiologic factors and complicating pathological changes, and may actually deceive so that cause and effect are not distinguishable. To exemplify the progression of a disease process, with its final possession of the characteristic qualities of two or more groups, one may utilize a case of congenital hemolytic icterus. Here, the primary defect lies in the red blood cell, with its increased fragility leading to increased destruction, and hence, over-production of bilirubin. The case clearly belongs to the hemolytic or superfunction group. With the excretion of a concentrated bile, the scene is set for the formation of bile thrombi or actual calculi of bilirubin or mixed type. These form and may cause variable grades of obstruction with its attendant symptoms and findings. Now, both the formation and excretion of bilirubin are disturbed. Furthermore, Rich[21] has pointed out that in the later stages of the disease, actual damage to the liver cell follows upon the long standing anemia, and its associated lowgrade anoxemia. Thus, the hepatocellular element is added with its disturbance in transferring bilirubin from the vascular to the biliary radicles. So, we have traced, in one disease state, progressive disturbance along the entire course of bilirubin production and excretion. Of paramount importance, however, is the understanding that the primary defect originated in the red blood cell and its ease of destruction by the cells of the reticulo-endothelial system. It is on this basis that this condition is classified as "hemolytic" icterus, and with a yardstick of these standards other icteric states are sorted.

The nature and implications of the Van den Bergh reaction now concern us, to aid its better utilization in diagnosis. This test, dependent upon the response of serum or plasma to the diazo reagent, yields differences of diagnostic import. A direct reaction which follows promptly upon the admixture of the serum and reagent is obtained with bile and the blood in icteric states associated with biliary obstruction or liver cell damage. The indirect reaction which requires the addition of alcohol is found in hemolytic types of icterus. The biphasic reaction is intermediary. The question was raised whether the different reactions were related to an altered composition of the bilirubin after passage through the liver cell. Several physical and chemical differences suggested that this might be so, namely, that direct bilirubin is oxidized more readily (Van den Bergh, Andrews); that it is more easily absorbed by the protein precipitate on alcohol precipitation (Van den Bergh); that it does not pass into solution with chloroform (Grunnenberg); that it is dialyzable through a collodion membrane (Hoover and Blankenhorn), which fact is probably related to the presence of bile in the urine in cases of obstructive and hepato-cellular icterus, and its absence in hemolytic icterus. Recent work indicates, however, that the "indirect bilirubin" may exist in the blood in combination with other substances. Feigl

and Querner suggest a lipoid linkage; Adler and Strauss, a protein combination. Thannhauser and Andersen claim that the addition of bile salts and cholesterol to an indirect bilirubin serum changes the reaction to direct; Stuber makes similar claims for uric acid. Barron's[22] informing work is of importance. He added to normal blood serum increasing amounts of sodium bilirubinate, giving direct Van den Bergh reactions. Up to 12 mgm. per cent, an indirect reaction was obtained; at 16 mgm. per cent, a biphasic reaction; above this amount, a direct reaction. He concludes that "some constituent of the serum has a tendency to absorb bilirubin . . . and prevents the immediate coupling with diazonium salts". A direct reaction would be obtained, therefore, when the amount of bilirubin present in the blood exceeds the absorbing ability of the important substances (probably serum globulin—Adler and Strauss; Barron), or substances are present in the blood (bile acids, cholesterol, uric acid) in large amounts, which by their stronger absorbability, prevent the absorption of bilirubin. The latter is then able to react immediately with the diazo reagent.

An understanding of the metabolism of urobilin also is necessary for proper analysis of its alterations in icteric states. Urobilin is the reduction product of the action of bacteria on bilirubin in the intestine (von Müller; McMaster and Elman[23]). Some is reabsorbed from the intestine and returned to the liver for future use in pigment formation, some reaches the general circulation and is excreted by the kidneys, traces being found normally in the urine. In the urine, urobilinogen is rapidly oxidized to urobilin. The threshold of the liver for urobilin is limited, and in the presence of liver cell disturbance, even the normal quantity cannot be cared for, more passes into the blood, and thus more is excreted in the urine. An increased urinary excretion also can be effected by an increased destruction of erythrocytes, with its increased production and excretion of bilirubin into the intestine, and therefore increased production of urobilinogen. Certain limitations of the diagnostic value must be noted: namely the increase in most acute infections where there exists no reason to suspect liver damage; the diurnal variation, more being excreted in the afternoon than in the morning; the failure of the kidney of chronic glomerulo-nephritis to excrete it, even in the presence of liver disease. It is evident that an increase of urobilinogen or urobilin in the urine can be utilized diagnostically only in conjunction with other clinical symptoms. Absence of these pigments in icteric states is, however, much more significant, indicating failure of bile to reach the intestine.

In attempting to differentiate clinically the types of icterus, our understanding of the extra-hepatocellular formation of bilirubin stands us in good stead. Proper appreciation of the fact that icterus may exist, independent of significant liver cell dysfunction leads us to utilize clinical data more efficiently. We are able to segregate the entire group of hemolytic or superfunction icterus from those related to disturbance in the hepatic epithelial cells and bile passages, i. e., production versus excretion. In the latter groups,

with icterus traceable to improper excretion of bilirubin, associated symptoms always are present pointing toward the liver as the seat of damage. In fact, not infrequently the patient directs attention to the liver area, in telling his story, covering it often with his hand. In catarrhal icterus, the vague digestive disturbances preceding the onset of jaundice, and the enlarged liver point the way. In obstruction to the ducts, the pain usually present, the tendency to acholic stools, etc., indicate the site of disturbance. The presence of itching favors this group. The Van den Bergh reaction is direct or biphasic; bile is present in the urine; urobilin may or may not be present, depending on the amount of bile which reaches the intestines. *In the group of hemolytic icterus,* where jaundice follows upon increased bilirubin production and a mere quantitative difficulty of liver cell excretion, *the icterus exists as a leading objective symptom. Any concomitant subjective complaints point entirely away from the liver toward the cause of the hemolysis and its effects.* This is probably related to the beforementioned fact that bilirubin, being the normal product of hemoglobin breakdown, is so well tolerated by the tissues and their cellular elements. In the congenital and acquired hemolytic icterus, the anemia and its consequences are outstanding; in the course of severe infections, it is merely an additional symptom; with chemical poisons leading to hemolysis, signs point toward this cause. The Van den Bergh reaction is indirect; bile is absent from the urine; urobilinuria is marked.

Is it possible further to analyze the functioning of the reticulo-endothelial system and lead to additional aids in diagnosis? Normally, as indicated before, the destruction of red blood cells and formation of pigment take place in the Kupffer cells of the liver and endothelial cells of the spleen and bone-marrow. The excretion of bilirubin via the hepatic epithelial cells keeps pace, maintaining a constant level in the blood. Abnormally, in icteric states, it is conceivable that the process of pigment production may proceed along normal or abnormal channels. In hepato-cellular and obstructive icterus, the bilirubin is still the product of members of the reticulo-endothelial system, normally engaged in the exercise of this function of pigment formation. In true hemolytic icterus, a mere overactivity of the normal agents is at fault. We must recognize, in addition, however, a sub-group of cases of "super-function" or "hemolytic" icterus, in which members of the reticulo-endothelial system, everywhere in the body, not engaged normally in this activity of bilirubin formation also assume this function (endothelium of the peritoneum, the lung, the skin).

Clinical facts appear to substantiate this differential conception. In hepato-cellular and obstructive icterus, days intervene between the onset of activity of the causative factors and the occurrence of visible jaundice. For example, in catarrhal icterus, a period of prodromal symptoms of from four to five days to a week or more is found before the onset of jaundice. In calculus obstruction of the common bile duct, a period of forty-eight hours or more intervenes before icterus appears, with the exception of patients in whom

cholecystectomy has been performed previously. In congenital hemolytic icterus one cannot always define the true time interval, but even here, following the so-called "crisis", a period of several days elapses between the onset of the pain and the appearance of the deeper jaundice. A definite interval is noted following the activity of hemolytic substances — chemical or bacterial. In all these conditions, after removal of the local or general causes, the jaundice persists for a shorter, or usually, longer period, related probably to the greater degree of hyperbilirubinemia and also the greater ease of penetration and tissue staining of the protein-free bilirubin compound. Consequently, the need exists for a more prolonged period of recession.

On the other hand, in icteric states consequent upon bilirubin-forming activity of portions of the reticuloendothelial system, not so engaged normally, differences are noted. If an extravasation of blood is slight, only regional icterus may follow, as in the skin following trauma. If moderate, as in an hemorrhagic effusion in the peritoneal cavity, or a moderate pulmonary infarction, moderate icterus is present. If a severe hemorrhage occurs within the body, universal icterus may occur. In icterus neonatorum, various gradations of this process may be seen, from small patches of regional icterus to complete jaundice (one of the main elements in this affection being the breakdown of red blood cells and actual formation of bilirubin by the endothelium of the skin). In all, the appearance of increased bilirubin (and associated pigments), locally and generally, is noted soon after the occurrence of the accident, usually only hours intervening. The discoloration in the skin appears soon after trauma (conjunctival hemorrhages alone remaining red until absorbed). Following massive hemorrhages into the peritoneal cavity as in ruptured ectopic gestations, or following large or multiple pulmonary infarctions, within six to twelve hours, the patient may be subicteric. The icterus of rapid appearance also has the faculty of rapid clearance, being gone very soon after removal of the causative factors.

It is essential, too, to note that disturbance in the bilirubin-excretory power of the liver cell may be of clinical importance in conditions where there exists neither visible jaundice nor latent jaundice, as evidenced by slight increase in the blood content of bilirubin. Interference with this excretory power of the liver is effected much more easily than with its numerous metabolic activities. In acute liver disease, all functions may be disturbed, often out of proportion to the degree of evident damage. In chronic disease, as cirrhosis, with its brunt of mesenchymal damage, the parenchymal cell slowly adapts itself to the acting forces, and evidences no disturbed function, unless taxed or overburdened. Proof of a relatively isolated dysfunction of the liver cell may then be demonstrated, by taxing the individual with ingested or injected bilirubin. Bergmann,[24] Eilbott,[25] and recently Harrop and Barron[26] considered "the bilirubin excretory power of the liver . . . the most delicate for testing the functional capacity of this organ". Retention was found in pernicious and other severe

anemias, acute infections, postarsphenamine and catarrhal jaundice some months after clinical recovery—all indicative of mild interference with liver cell function.

Although the bilirubin-excretory test does indicate some hepatic cell dysfunction, it must be appreciated that this sudden over-burdening of the liver cell with bilirubin by far overexaggerates the method of occurrence of icterus within the body. The rôle played by the epithelial cell in the development of an "hemolytic" icteric state cannot be accurately inferred from the result of this test.

It should be evident that the present conception of the physiologic principles underlying the formation of bilirubin and the causation of icterus has led us far from the old Minkowski-Naunyn dictum, "without liver, no jaundice". Extra-hepatic production of bilirubin makes possible the development of icteric states, by forces acting entirely or mainly outside the liver. The importance to be ascribed to associated changes in the liver cells, as found by Rich, is still not definite. Certainly, they may aid in the progress of jaundiced states, but whether they are present, or needed, at its inception is questionable. Clinically, as indicated, one is justified in separating entirely, those groups of icterus due to causes, active intra- or extra-hepatically. The presence in the former of associated symptoms indicating liver disturbance and the absence in the latter of any subjective complaints pointing toward such dysfunction are facts of important diagnostic value.

Summary

1. Jaundice as a leading objective symptom, when due to over-production of bilirubin exists free of any complaints pointing toward liver dysfunction. Any associated symptoms or signs reflect the cause of the hemolysis and its effects.

2. When jaundice follows disturbed function of the hepatic epithelial cell or obstruction of biliary ducts, signs point toward the liver as the seat of damage.

3. It is suggested that the group of "hemolytic" or "superfunction" icterus may be divided clinically, dependent on whether the abnormal quantity of bilirubin is the product of members of the reticulo-endothelial system normally engaged in this production (liver, spleen, bone-marrow) or abnormally so functioning (endothelium of skin, peritoneum, lung, etc.)

4. The bilirubin-excretory power of the liver cell may be utilized as an excellent test of liver function. Prolonged retention of injected bilirubin may be the only demonstrable evidence of a cellular dysfunction.

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Niemann-Pick's Disease*†

(Essential Lipoid Histiocytosis)

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NIEMANN-PICK'S disease is a disease of infancy characterized clinically by an enlargement of the liver, spleen and lymph glands, associated with yellowish brown pigmentation of the skin and accompanied by an enlarged abdomen and more or less emaciation. Cranial and skeletal changes may be associated. It is a fatal condition, being characterized by progressive wasting. Death may be due to intercurrent affections. "It is a congenital, familial, constitutional, systemic disease which manifests itself as a disturbance of the lipoid metabolism and leads to a deposit of complex cellular substances in the cells of the reticulo-endothelial apparatus. Its etiology and pathogenesis are unknown. It does not yield itself to therapy."[1]

In 1914, Niemann[2] described a peculiar form of splenohepatomegaly, occurring in an infant, which was fatal at eighteen months. Since that time, several cases have been reported. Extensive clinical and pathological studies have been made. These include cases reported by Knox, Wahl and Schmeisser,[3] Siegmund-Köln,[4] Bloom,[5] Henschen,[6] Schiff,[7] Hamburger,[8] Corcan, Oberling and Dienst,[9] Berman,[10] Kramer,[11] Dienst and Hamperl,[12] Abt and Bloom,[13] and Abrikossoff[14].

Berman, in his report of a case in a girl of fifteen months, records the history of vomiting and abdominal distention since the second month of life. Enlargement of the liver and spleen was recognized at six months. Splenic puncture showed typical foamy cells and, at autopsy, the splenic pulp was found to be made up almost entirely of foamy cells, large, round, vacuolated and pale. He also reported a fractional determination of the blood lipoids.

Kramer's case was of a girl of fourteen months. The spleen had been enlarged since she was four months of age. Examination of the spleen, after a splenectomy, showed the tissues almost completely replaced by masses of large, pale cells of varying shapes with small nuclei.

Abrikossoff's case showed a moderate enlargement of the spleen and extensive involvement of the cranial and general skeletal structures. This, perhaps, justifies the assumption of a skeletal type of Niemann-Pick's disease after the manner of a skeletal type of Gaucher's disease.

Bloom and Kern[15] concluded, from chemical analysis of the spleen, that, in

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*Received for publication, September 2, 1931.

Niemann-Pick's disease, the stored material is chiefly phosphatids, probably lecithin and cholesterol. While in Gaucher's disease, the stored material is kerasin.

In both cases, these pathological substances are deposited in the liver and spleen causing a marked enlargement of these organs.

The composite clinical picture presented by Abt and Bloom[13] might, in many respects, be that of our case. The patient was mentally and physically retarded. The facies strongly suggested mongolianism. He could not stand; when he assumed a sitting posture, the head and shoulders drooped forward exhibiting a decided curve of weakness. There was little interest manifested in what went on about him. Toys held no allurement. For the most part, he was content to lie quietly taking only a brief interest in the attendant, other children at play and even in his food. The temperature fluctuated, and his leukocytosis reached 22,400. The accompanying photographs portray the mongoloid appearance and the large ascitic abdomen. (Figures 1 and 2.) After tapping, the decidedly enlarged liver and spleen were found to extend as low as the crests. (Figure 3.)

Palpation and x-ray of the spine demonstrated an abnormality, probably a congenital defect. X-ray of the chest revealed alterations of the ribs, probably the bony involvement to which

Fig. 1 Mongoloid appearance, ascites, and edema of scrotum in patient with Niemann-Pick's disease.

Fig. 2. Marked ascites associated with hepatosplenomegaly. Niemann-Pick's disease.

Abrikossoff[14] called attention. An abnormal condition of the maxilla might be congenital or, more probably, further evidence of bony change indicating cranial involvement.

Case Report

Frank S., white, Austrian, twenty months old, was admitted to the Children's Department of the Washington Hospital, August 24, 1929, because of an enlarged abdomen.

Five weeks prior to admission, he had an acute febrile disorder accompanied by an eruption which was probably measles. Two weeks before admission, the mother noticed his abdomen "seemed swollen" and had become progressively larger. At about the same time, she noticed that he was slightly jaundiced.

Past History. He was born December 13, 1927. Labor was easy, delivery spontaneous. There were no birth injuries, cyanosis, hemorrhage or convulsions. He was the fourth child, full term, breast fed until admitted to the hospital. He had had no previous illness except measles. He sat up at eight months; first tooth erupted at ten months. His first words were spoken at one year. At fifteen months, he was able to stand, using his crib as support. He was able to take a few steps at the age of seventeen months.

Family History. Father, mother and two sisters living and well. One brother died three days after birth; cause unknown. Neither of the two sisters shows any abnormality nor is there any history of illness comparable to the patient's disease in either the paternal or maternal families.

Physical Examination. He was a rather poorly nourished and developed child of about twenty months, whose mental development seemed below that of the average in-

Fig. 3. The same patient after withdrawal of the ascitic fluid.

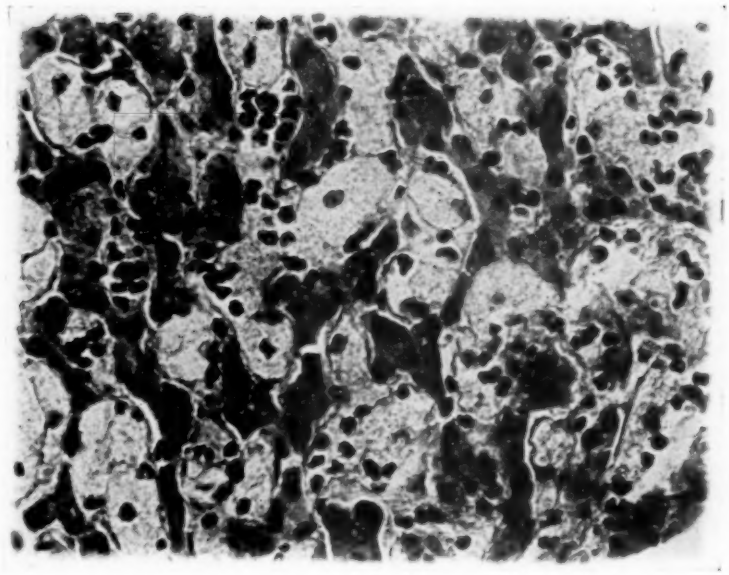

FIG. 4. Cholesterolosis of reticulo-endothelial cells of liver sinusoids.

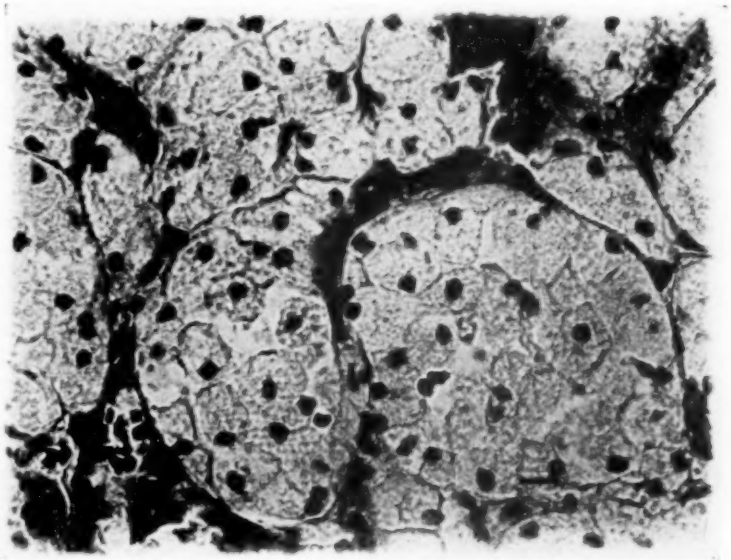

Fig. 5. More marked separation of liver cells by masses of foam cells representing the reticulo-endothelium of the intercordal sinusoids.

fant of this age. There was a slight yellowish pigmentation of the skin. The head was of the square type and seemed somewhat large in proportion to the rest of his body; circumference 50 cm. The anterior fontanel was almost closed. The sclera was distinctly visible above the cornea; the pupils were equal and reacted to light. Ears were negative. There was a marked mucopurulent discharge from each nostril; teeth were poorly developed and irregularly spaced; the alveolar process, on the left, was widened and partially covered with a white exudate. Tongue was thickly coated with a grayish brown exudate. There was mild inflammation of the mucous membrane of the pharynx. The anterior and posterior cervical glands were palpable. There was a questionable rigidity of the neck; the thorax seemed flattened antero-posteriorly and the costal margins flared outward and upward. The lungs were resonant, breathing was not labored but respirations were accompanied by distress. The apex beat of the heart was in the fourth intercostal space in the mid-clavicular line; impulse was barely felt; the sounds were clear and regular. The abdomen was markedly distended, showing many dilated veins. The abdominal wall was tense; there were signs of fluctuation; no masses could be felt. Genitalia were normal except for first degree hypospadias. The vertebral column showed a prominence in the lower lumbar region. It was widened and irregular. Bony prominences were felt laterally to the spinal processes which seemed to be more widely separated than normal. The extremities were swollen. The surface temperature of the hands and arms was below normal but less than that of the feet and legs which was distinctly cold. There was some swelling but no pitting on pressure. The reflexes were diminished or absent. By high rectal examination, a mass could just be felt.

The day following admission, respirations were more embarrassed and the abdomen was tapped and 3200 c.c. of straw colored fluid was removed, following which he was relieved. The abdomen was quite flaccid. The liver and spleen were both enlarged. The liver could be felt as low as the umbilicus in the midline and extended downward almost to the crest of the right ilium. The spleen extended downward almost to a corresponding point on the left. Both masses were firm, hard and smooth with the exception of a nodule which seemed to be attached to the outer surface of the spleen.

Two weeks later, the abdomen seemed to be refilling. The head appeared larger; the circumference was 50.5 cm. The child took very little interest in his surroundings and was not eating well.

On September 18, the abdomen seemed to be increasing in size. The circumference of the head was 50.1 cm. Its maximum of 51.2 cm. was reached one month after admission.

The spinal fluid was clear; globulin was increased; no increase in cells. Kahn test on the spinal fluid was negative. His blood picture, on admission, was: Hemoglobin, 75 per cent; red blood cells, 4,530,000; white blood cells, 7,100; polymorphonuclears, 68 per cent; lymphocytes, 24 per cent; endothelial leukocytes, 4 per cent.

There was a progressive change from this picture to that of February, 1930, which was: Hemoglobin, 65 per cent; red blood cells, 3,420,000; white blood cells, 22,400.

The urine showed at intervals a trace of albumen and, at times, rather numerous hyaline casts with some few white blood cells.

Aside from a mild bronchopneumonia in November, 1929, there was nothing unusual in his progress. He lost weight intermittently and failed rather steadily throughout the course of the disease which was terminated by death, February 22, 1930, almost six months after his admission.

Pathological Report. The body is that of an emaciated child approximately two years old. The feet, legs, scrotum and penis are edematous. Congenital defects present are hypospadias and occult spina bifida in the lumbar region. There is marked distention of the abdomen and eversion of the costal margin. The head is large and square. The anterior fontanel is not completely closed. There is a deficient growth of hair on the head. The face has an aged appearance. Palpation gives one the impression of a mass below the right costal margin. There appear also to be masses in the lower abdomen.

The lungs are pale and grossly do not show

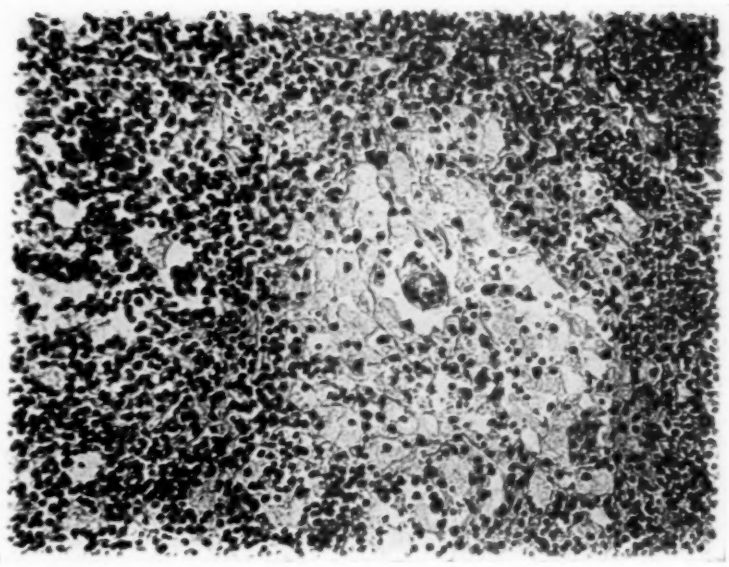

FIG. 6. Groups of foam cells, lipid-containing reticulo-endothelial cells, in the spleen.

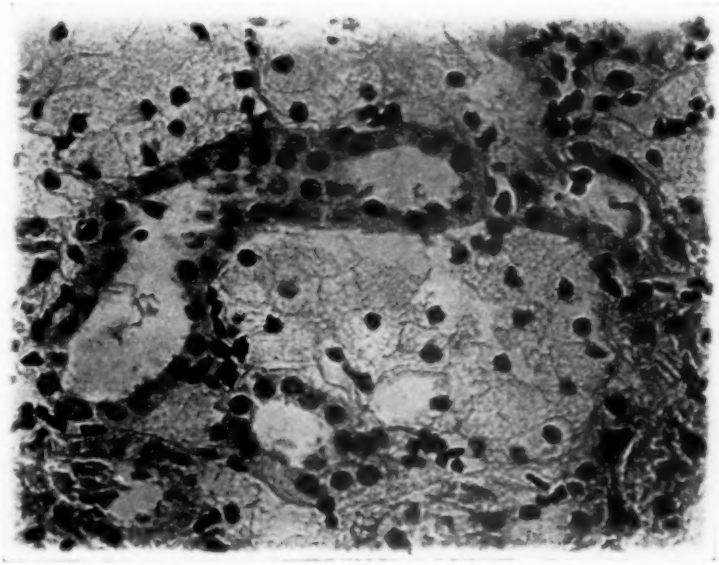

Fig. 7. Intertubular masses of foam cells in the kidney.

suggestive changes. The lymphatic glands at the hilus are enlarged.

The heart has a pallid appearance but otherwise shows no pathological lesions.

The intestines are matted together and adherent to the parietal wall. The adhesions are dense and difficult to break up. Between the coils are found pockets of clear, yellowish colored fluid which is partly coagulated. The mesenteric and retroperitoneal lymph nodes are enlarged.

The liver is covered with a thick, grayish white membrane and is adherent both to the intestine and diaphragm. Separation of these adhesions is difficult. The organ is enlarged, especially the right lobe. On the under surface of the right lobe, there is a longitudinal fissure in which there is a grayish white nodule one centimeter in diameter. On section, the liver cuts with increased resistance and the cut surface bulges. The cut surface is of a pale, grayish color, with a mottling of irregular lighter areas.

The spleen is only moderately increased in size and shows a marked hyalo-capsulitis. On section, it cuts with increased resistance, the cut surface bulges and is of a dark red color with small irregular patches of a paler hue. The splenic corpuscles are indistinct.

The kidneys are of approximately normal size, pale, and the capsules strip readily. The cut surface is pale with a mottling of lighter areas. The medullary rays and pyramids are indistinct.

The spinal canal was opened at the point of the spina bifida and was found to contain a large quantity of clear yellowish fluid, partly coagulated. Gross lesions were not found in the cord.

The cortex of the ribs is thin and friable. The cancellous tissue is rarefied and paler than normal.

Microscopical Examination. Sections from all the organs examined show extensive involvement with large, flat, irregular, round or polyhedral cells having small nuclei which are usually eccentrically located. The cell cytoplasm is finely granular, vacuolated and shows a delicate reticular structure. These cells apparently have their origin from the reticulum lining cells of the various organs.

Sections from the lungs show irregular groups of alveoli distended with these cells and compressing adjacent capillaries. The larger vessels are surrounded by wide mantles of the cells which have replaced the adventitia and the greater part of the media while the intima remains intact.

Sections from the liver show a diffuse involvement. In the periportal tissue the bile ducts and blood vessels are surrounded by these cells. In the parenchyma, the sinusoids are distended, the adjacent cells compressed and atrophic (figures 4 and 5). Wide areas show complete absence of liver cells, the new cells lying in a reticulum consisting of remnants of the walls of the sinusoids. In the nodular area, the cells are growing either diffusely or in small and large alveolar formation. Here also, the cells lie in a reticulum arising from the walls of the sinusoids.

Sections from the spleen (figure 6) show involvement of the capsule, pulp and splenic corpuscles. The cells are found about and within the corpuscles and in many cases only a trace of the lymphoid tissue remains. The splenic venules are involved in small and large irregular areas. The venules surrounding the involved parts are engorged with blood.

In the kidneys (figure 7) the cells are found growing either diffusely or in small and large alveolar arrangement surrounded by a delicate limiting membrane which is apparently derived from the kidney reticulum. In the involved areas these cells have largely replaced the kidney tubules. The glomerular tufts are also involved, practically all showing partial destruction of their normal structure and replacement with these new cells.

In the spinal cord, the cells are packed around the nerve elements which are degenerated and atrophic, many having disappeared completely.

The reticulum of the sympathetic ganglia also shows large groups of the characteristic foam cells (figure 8).

Sections from the ribs show the cortex thinned and immediately beneath it broad sheets of large pale cells surrounding a few fragments of bone trabeculae. Centrally, very little bone structure remains (figure 9).

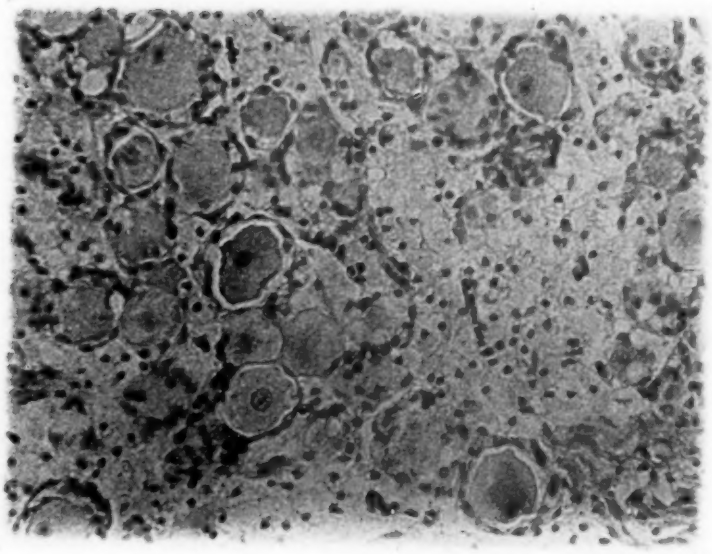

FIG. 8. Sympathetic ganglion with foam cells in the reticulum.

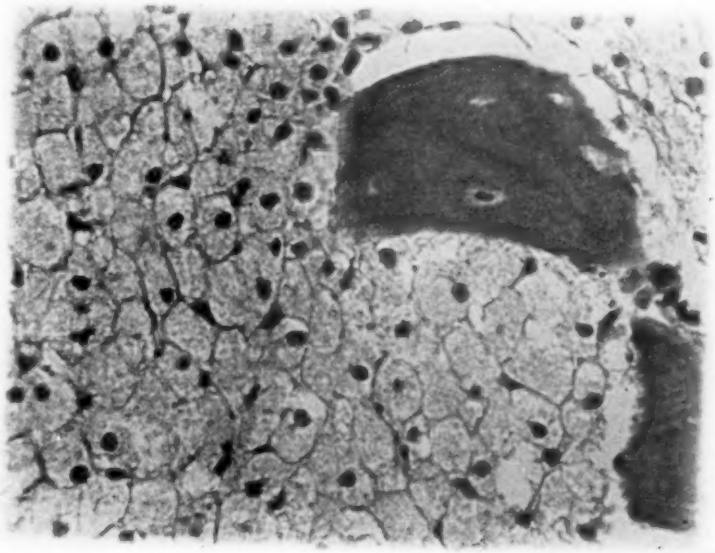

FIG. 9. Osteoporotic bone with marrow entirely replaced with foam cells.

The blood forming islands are invaded and greatly reduced in number. There is no evidence of osteoclastic activity by these cells but rather bone destruction seems to result from pressure atrophy.

Sections from a lymph node show the normal architecture destroyed. The new cells lie in a reticulum derived from the original structure. Only traces of lymphoid cells remain.

After mordanting the sections with bichromate of potassium, the fat in the cells takes a dark yellow stain with scarlet red and appears both as minute and medium sized globules.

A consideration of the extensive involvement of the various organs, the evident relationship of the cells to the reticulo-endothelial system, the presence of fat in the cells and the absence of iron reaction as in Gaucher's disease, together with the age and early fatal outcome would seem sufficient evidence to establish this as a case of Niemann-Pick's disease.

Acknowledgment of our appreciation is hereby made to Dr. F. I. Patterson, who contributed to the care of this child.

Photomicrographs accompanying this article were made possible through the courtesy of Dr. E. T. Bell and his staff of the University of Minnesota.

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Four Physiologic Defenses of the Upper Part of the Respiratory Tract: Ciliary Action, Exchange of Mucin, Regeneration and Adaptability*†

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I SHALL give the results of some studies in connection with a tremendously interesting and but poorly understood structure; namely, the mucosa of the upper part of the respiratory tract. This work resulted from a study of the common cold.[3] In connection with that, the textbooks and periodicals were thoroughly searched for an adequate discussion of the physiology and pathology of the nasal mucosa. Nothing satisfactory was found anywhere. Consequently, I began a special physiologic study.

In this presentation, four factors in the armamentarium of defense of the nasal mucosa will be considered. They are ciliary activity, exchange of mucin, regeneration, and what might be termed adaptability to environment. The regeneration meant is that repair which follows injury to the surface, as in the common cold.

The purpose of the presentation is to emphasize the great activity of this extremely delicate and much exposed membrane. I think there is no structure in the body so delicate and so severely exposed to the environment as the nasal mucosa. One would expect an inert, resistent, leathery type of epithelium in such an exposed position. Instead there is a highly specialized, ciliated, fragile membrane. It exists, I believe, largely by virtue of its remarkably active systems of defense.

Ciliary Activity

Ciliary activity in general is well understood. Biologists and physiologists have developed the knowledge of this phenomenon in great detail. This knowledge, however, has not been applied to the nasal mucosa in an adequate fashion. Its importance has not been sufficiently stressed.

The motion of the cilia of the nasal mucosa of man is simple, whip-like, and in two phases; there is an active phase in the direction of the flow of over-lying material, and a phase of recovery. The rate is approximately 250 cycles a minute. The action is coördinated in a very remarkable manner. When viewed in profile, the cilia are seen to beat in sequence in such a way that waves are formed, similar to those seen in a field of grain when the wind passes over it. No two cilia in a given

*Read before the American College of Physicians, San Francisco, California, April 5, 1932, with motion picture demonstration.

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wave are in exactly the same phase at any moment. When viewed from the front, on the other hand, rather small groups beat in unison. In military language, the ranks beat in unison and the files in sequence. In larger fields observed from above, I have received the impression at times that they are divided into strips that coördinate in such a way that adjacent strips beat more or less alternately. This would provide a hand-over-hand action that would greatly increase the effectiveness of the cilia in moving along the covering film of mucin. It is difficult to make certain that this hand-over-hand action is normal because it can be seen distinctly only when the ciliary beat is abnormally slow. The power of ciliary action is much greater than is ordinarily supposed. These tiny, hair-like processes, only five or six microns in length, move comparatively huge loads of overlying material that may be more than a hundred times as thick as the length of the cilia. The efficiency of ciliary action increases under loads until an optimal pressure has been exerted, and then decreases. The optimal pressure in the case of the epithelium from the pharynx of the frog is said to be about twelve grams per square centimeter.[7] It is said to be less in the nose of man. In any case, the weight of the secretion in a mucin-filled maxillary sinus would not be sufficient to depress ciliary action on the floor, but would serve rather to stimulate it.

The question of ciliary control has not been settled. The action itself is automatic. Detached cells continue active, and even single detached cilia will beat if a bit of cytoplasm remains attached to them, as can be seen in motion pictures that I have made. In addition to the automatic action there must be a control of some type in order to produce that remarkable coördination. Whether it be nervous[8] or on some other basis,[9] is of no particular concern in this presentation.

Exchange of Mucin

The speed of ciliary motion is bound up with the nature and the depth of the overlying film. Normally, the moist film that covers the nasal surfaces is a very thin, rather highly viscid, mucinous secretion. In a sense it is like one large, intact membrane or web that overlies all surfaces within the nose, sinuses, pharynx and esophagus. This web moves throughout its extent continuously. It has a certain tensile strength, and can sustain traction. This is a very important feature. There are some regions within the nose that normally are nonciliated. The web of mucin moves across these by means of traction exerted on it by the ciliated regions. From my studies it appears to me that this traction on the mucin is one of the most important factors in the successful accomplishment of normal drainage of the nose and sinuses. Gravity, on the other hand, plays only an incidental part, and is often a handicap rather than an aid.

The web of mucin moves backward within the nose over a fairly definite system of drainage, at widely varying rates of speed.[5] Both rate of speed and direction are determined largely by the relation of the ciliated to the nonciliated areas. The regions in which the inspired air first makes impact are nonciliated.[6] These vary somewhat in position and extent, according to indi-

vidual anatomic variations, but in general include the preturbinal region on the lateral wall, the anterior ends of the middle and inferior turbinates, and the anterior fourth of the septum. The presenting surfaces of spurs and ridges may likewise be nonciliated. The remaining surfaces, including the posterior two-thirds or three-fourths of the nose (exclusive of the olfactory region) are ciliated. In these studies the system of drainage was mapped by dotting drops of India ink over the surfaces and observing the direction and rate of flow as they moved back to the nasopharynx. The rate of flow over the ciliated areas was found to be comparatively great; namely, four to six millimeters a minute, whereas over the nonciliated areas, it was only a few millimeters an hour.

The direction of flow in the ciliated regions in general was backward, with a slight downward tendency. Over the middle and inferior turbinates there was found a strong tendency for the flow to be diagonally downward, across the inferior border, into the corresponding meatus (figure 1). Apparently the reason for this is that the cilia are more active in the protected middle and inferior meatuses than in the more exposed, common meatus. In those regions, then, the web of mucin moves faster, and through traction drags the mucin from the areas of slower motion on the mesial side of the turbinates into the meatuses. It follows that the mucin does not necessarily flow exactly in the line of the direction of the beat of the cilia immediately underlying. Through traction it may slide diagonally across that line.

The direction of flow in the nonciliated regions appeared to be determined almost entirely by traction from the middle and inferior meatuses (figure

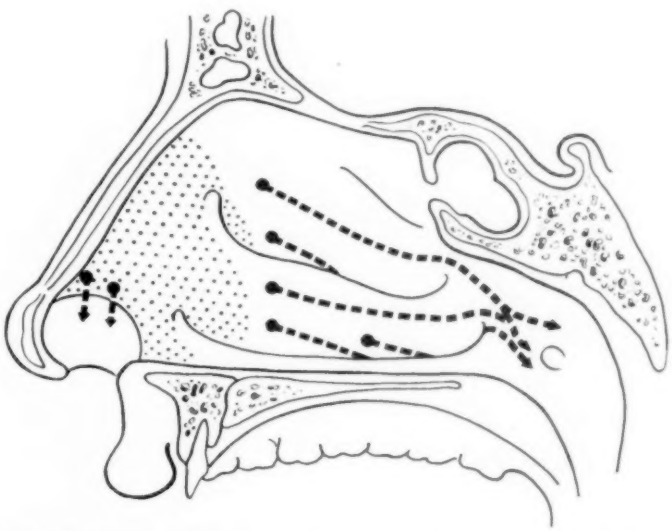

FIG. 1. The direction of the normal flow of mucin over the ciliated surfaces on the lateral wall of the nose. The flow along the indicated lines is rapid. The stippled area is nonciliated.

2). The motion was very slow. The lines followed by the ink converged at the anterior attachments of the turbinates and disappeared into the meatuses to emerge at the posterior ends. In a word, the nonciliated, inactive areas on the lateral wall drain very largely through the inferior and middle meatuses. It is to be remembered that this is the region in which dust, bacteria, cosmetics, and other foreign materials are most likely to lodge. Therefore, this foreign material drains back through the meatuses.

The drainage on the septum was found to be similar to that of the lateral wall. There was an inactive, nonciliated area anteriorly that drained very slowly through traction exerted on the web of overlying mucin. The rate was only a few millimeters an hour. Behind this area the surface was found to be very active (except on ridges and spurs) and ink drained at the rate of three to six millimeters a minute. It took from only three to ten minutes for the ink to traverse the distance from the anterior third of the septum to the posterior margin.

In general, then, it may be said that the mucinous film covering the surfaces of the posterior two-thirds of the nose is replaced every ten or fifteen minutes. The film over the anterior third is renewed only about once each hour or two, and drains away through the meatuses. This may explain the fact that cultures made from deep in the nose are so often sterile.[1] Very few bacteria lodge deep in the nose, and those that do lodge there are swept away quickly. The regions where they lodge in large numbers drain very largely through the meatuses, where cultures are not usually taken.[4]

Rapid Regeneration

Microscopic studies of warm, fresh secretion derived from patients with early colds, and of specimens removed

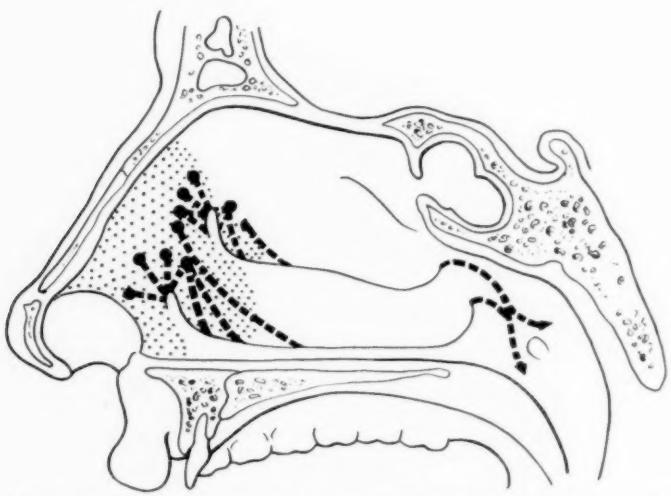

Fig. 2. The direction of the normal flow of mucin as it is drawn by the cilia of adjacent areas over the nonciliated mucous membrane in the anterior portion of the nose. The lines converge at the anterior attachments of both turbinates, indicating that the mucin is drawn into the meatus.

for biopsy in the course of colds indicate clearly that there is extensive loss of the cells from the lining mucous membrane in the course of the common cold. In the first three days there are often great numbers of living ciliated and nonciliated epithelial cells floating free in the secretion (figure 3). During these days such cells greatly exceed the leukocytes in number. The nonciliated forms are the immature replacement cells normally found deep in the epithelium. Their presence indicates that the destruction goes deeply into the epithelium. This has been found to be the case in specimens removed for biopsy. Sometimes there is only a single layer of cells left in place on the basement membrane.[8] Yet it is rare that true ulceration occurs or that the underlying tissues are destroyed. It is inferred that the epithelial cells slough out in response to surface irritation and are replaced repeatedly with facility and great rapidity. The injury goes deep into the epithelium and causes extensive destruction, yet in a few days the epithelium is once more entirely normal.

Adaptability

The finding of active and inactive areas of drainage within the nose, and the determination that the mucous membrane of the active areas was ciliated and that of the latter nonciliated,

Fig. 3. Epithelial cells and leukocytes found in the secretion on the third day of a cold. Most of the cells are epithelial cells.

suggested study of histologic changes in the epithelium after the normal ventilation had been altered experimentally. The point to be determined was whether the various types of epithelium within the nose and sinuses are produced by variations in exposure to flow of air in the individual case, or whether the inference is that they are produced only by long ages of evolution. Two series of experiments were performed. The results indicated clearly that the nasal mucosa has a chameleon-like property of altering its form radically, according to circumstances.

In one series of experiments the right nostril of each of eight rabbits and of two dogs was closed surgically, causing the animals to breathe through one side of the nose only. The animals were killed after periods varying from three weeks to six months, and sections from various parts of the nose were examined microscopically. There were marked changes on both the open and the closed sides in the rabbits. In the dogs there were marked changes on the open side only.

The histologic alterations on the septum on the side of the open nostril were in the nature of an extension backward of the area of squamous-like epithelium normally found just posterior to the vestibule. In those animals that lived longer, this type of epithelium extended well over half the length of the septum. The cilia were lost and the cells became stratified (figure 3). Going further backward, it was found that the epithelium became transitional and finally columnar. The mucous membrane of the elaborate turbinate became stratified and very much thick-

FIG. 4. Section through the nasal septum of a dog four months after surgical closure of one nostril. The epithelium of the open side is uppermost. There is a marked change from the high columnar of the closed side to the squamous-like epithelium of the open side.

er than normal. In the meatuses the cuboidal epithelium became columnar, and short columnar epithelium became tall columnar. Within the sinuses there was practically no change. In a word the degree of change was proportional to the exposure to the impact of inspired air.

In the rabbits there was a very marked change on the closed side also. The distribution was similar to that of the changes on the open side; greatest on the anterior part of the septum, and least within the sinuses. It consisted in a very great increase in the numbers of goblet cells; that is, nonciliated, mucin-filled cells. Over the anterior portion of the septum every cell, practically, became a goblet cell some months after closure of the nostril. Further back on the septum, ciliated cells also appeared. About half way back there were equal numbers of ciliated and goblet forms, and the further back the examination was carried the greater the number of ciliated cells and the fewer the number of goblet cells found. There was also a marked increase in number of goblet cells over the turbinates; the number became progressively less marked posteriorly. This increase in goblet cells was not noted within the sinuses.

In another series of experiments the frontal sinuses of a number of dogs were fully exposed to the outer air by removal of the roof and overlying skin. This sinus epithelium also changed markedly. It changed from cuboidal to columnar in the spots that were best protected and became stratified in the most exposed spots.

These experiments indicate several things. First, it seems certain that the epithelium can alter its form radically in a comparatively short time, according to the demands made on it, and the various pictures of epithelium found do not represent different types of epithelium, but merely various forms of the same general respiratory epithelium. These experiments point to a probable explanation of the islands of squamous epithelium so commonly found in the trachea. Doubtless there are eddies in the streams of respired air that strike the tracheal wall with some force in those areas. The fact that there was no change in the sinus epithelium, either on the closed or on the open side in the series of cases in which one nostril had been closed, indicates that ventilation of the ostia of the sinuses may not be as essential as has been believed. The accidental finding of the tremendous increase in mucin-containing cells suggests the possibility that goblet cells represent only a phase in the life cycle of the ciliated columnar cell. Perhaps instead of two types of cells in this epithelium there is only one type.

Summary

The epithelium of the upper part of the respiratory tract is not simply a static structure, with a feeble tendency to move overlying materials. It is dynamic. It is intensely active. The cilia beat with extreme rapidity and move tremendous loads of mucin and foreign material with speed, power, and efficiency. The ciliary motion is dependent on the overlying film of mucin that is so much like another lining membrane. In the major portion of the nose this film of mucin is changed very

frequently. It may be said that there is a complete new lining over all the ciliated areas every ten or fifteen minutes. These portions are generally sterile. Even the nonciliated, inactive areas in the anterior fourth of the nose have an exchange of mucin every hour or two. When an irritant attacks from the surface, the mucosa sloughs its injured cells readily, before they are dead, and replaces them very quickly. Prolific regeneration seems to be part of the physiologic process. Under certain conditions the percentage of goblet cells contained can be made to increase very greatly. When very much exposed to the force of flowing air and foreign particles, the epithelium of the membrane is altered in form from ciliated columnar to squamous-like. It ceases its tremendous activity, and becomes passively resistant and inert.

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Paranasal Sinusitis
A Problem in General Medical Practice*†

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THE etiologic relationships of paranasal sinusitis** to systemic disease belong to the unsolved problems of clinical medicine. This is shown by the relatively increasing frequency with which patients suffering from conditions which may be referable to sinus disease find their way into the hands of consultants. The possibility of sinusitis as a causative factor must occur not infrequently to every physician who sees in chronic localized infection the solution of a considerable number of obscure diagnostic and therapeutic problems. Occasionally gratifying results have followed treatment advised on the basis of sinus etiology. However, failures have been so disappointingly frequent that skepticism and prejudice have tended to so displace rational thinking in the minds of many physicians, that some have come, as a matter of principle, to denounce almost all forms of sinus surgery. This unsettled state of affairs would seem to arise from:—(1) lack of adequate routine study and evaluation of the sinuses in common clinical conditions, (2) lack of and slow diffusion of knowledge of sinus physiology and pathology, (3) lack of recognition by internists and rhinologists that many of their problems are mutual and require enlightened cooperation for their solution, (4) technical misconceptions and inadequacies.

The following are some of the symptom complexes we have seen associated with sinus disease in which it seemed reasonably certain to us that the sinusitis was a determining or aggravating factor: (1) Headaches, acute and recurrent, "nasal ganglion syndrome"; (2) "Eye strain"; (3) Febrile states simulating typhoid, endocarditis, low grade sepsis; (4) Toxic conditions—athrepsia, marasmus, debility, certain anemias; (5) Bronchitis, acute and chronic (occasionally misdiagnosed as tuberculosis), bronchiectasis, lung abscess; (6) Allergic troubles—asthma, hay fever; (7) "Fag", "thick-head",

*Presented at the San Francisco Meeting of the American College of Physicians, San Francisco, April 5, 1932.

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**The subject matter has to do almost entirely with chronic hyperplastic sinusitis. While acute empyema of one or more sinuses is not uncommon, empyema is quite often a suppurative phase of chronic sinusitis. Acute suppurative conditions must be handled conservatively. Time and observation will often decide whether a simple acute process or an acute suppurative phase of chronic hyperplastic disease is present.

asthenia, neurasthenia, mental disorders; (8) Focal complexes such as arthritis, myalgia, nephritis, myocarditis, neuritis, herpes, "colitis", etc.; (9) Tic convulsif, spasmodic torticollis, "athetoid conditions".

Obviously sinus factors will be much more frequently diagnosed if they are suspected. Certain "leads" will be found useful in directing attention to the sinuses as a possible source of trouble, such as: (1) Any of the sinusitis complexes mentioned above; (2) Facies: "dull, puffy, weary eyes", "swollen nose and face", mouth breathing, nasal twang; (3) History of onset with a remote or recent "flu", with repeated colds, or following dental extractions; of undue sweating and chilliness; (4) History of chronic catarrh with nasal discharge or pharyngeal dripping; (5) Lateral pharyngeal lymphangitis, pharyngitis with visible mucoid, muco-purulent or purulent secretions in the nasopharynx; (6) Cervical adenopathy, especially of posterior chains.

The diagnosis of a sinus factor in systemic disorders should be made only after a complete clinical survey. The making of a diagnosis of a responsible sinusitis without the help of the rhinologist should be encouraged. It promotes independent thinking, prevents servile acceptance of "specialized" opinion, and helps to place the therapeutic decision on the shoulders of the general physician, where it belongs. It makes available advice based on the study of the patient as a whole. The fact that a chronic sinusitis is present is merely of interest; whether he who has the sinusitis suffers general ill health as a consequence of his sinusitis is another matter.

Roentgenology is by far our best objective method. The roentgenologist who takes pride in the accuracy of his positions, in the correctness of his exposures, and in the quality of his photographic work is a valuable ally. Opinions, even of highly trained and experienced roentgenologists, who are inclined to substitute interpretative skill and experience for poor films should be accepted with reservations. A word should be said for the use of a "scout" plate in the Waters position, even when there is little reason to suspect trouble. A normal film in the Waters position will go far toward ruling out a chronic sinusitis. If the clinical evidence still points to the sinuses a thorough rhinological examination with films in additional positions, with or without lipiodol, may be necessary. The general physician should acquire experience in film reading that his patient be not subjected to the liabilities of highly specialized interpretations. Finally, the platitude must not be forgotten that roentgenography reveals merely disturbances in densities and contour at a given time, and tells us little of the nature or behaviour of the pathological conditions present. The clinical records are often of more value than the ray findings. Occasionally repeated roentgenological studies are necessary to reach a decision. Such examinations are especially useful when allergic swellings of the sinus mucosae are in question.

Study and observation of the patient over considerable periods of time may be required. It may be necessary to follow his trouble through several recurring cycles in order to ascertain whether there is a hook-up between the patient's general and local symptoma-

tology. The failure of rest, appropriate hygienic measures, or a change of climate to bring the patient back to normal and keep him there, seasonal variations, and exacerbations in the patient's ill feeling with increase in upper respiratory symptoms are all significant. The disease history of chronic sinusitis has not yet been written. Its relationships to allergy, diet deficiencies, endocrine disorders, climatic factors, superheated moisture-poor air, repeated colds, and to fatigue and exposure are not well understood. Obviously the problem is large, the solution difficult, and it calls for continued and comprehensive studies.

There seems to be a lag in our knowledge of sinus pathology. There is little on the subject in the text books. The three volume English version of Kaufmann devotes less than a page to inflammatory disease of the sinuses. The sinuses are rarely investigated at autopsy and then only at the request of the clinician. Yet Harke[1] found 138 instances of gross inflammation of the paranasal sinuses in 395 autopsies. It would be interesting to see what change a routine postmortem exposure of the paranasal sinuses might work in our medical thinking on such subjects as lung abscess, meningitis, asthma, bronchiectasis, endocarditis, nephritis, and obscure septic and toxic conditions. In autopsies on deaths from asthma in which symptomatology referable to the upper respiratory tract is the rule, the sinuses have received scant attention. In the study of three cases of bronchial asthma with detailed postmortem analysis Kountz and Alexander[2] do not mention the sinuses. Huber and Koessler,[3] in their well known analysis of the pathology of fifteen cases from the literature and six personal cases in which they have confined themselves largely to the microscopic examination of the lungs, mention the paranasal sinuses only once:—"Catarrhal rhinitis with retained mucus in the left maxillary sinus" in a case reported by Marchand.[4] In Wright's[5] case, although the calvarium was removed, and although the clinical history pointed to a chronic sinusitis, there is no record of the paranasal sinuses having been examined at the autopsy.

Some of our lack of autopsy knowledge of paranasal sinus disease may be attributed to the want of any convenient method of exposure. The chisel is unsatisfactory and the sagittal head-splitting technique of Harke, although providing satisfactory exposures, gives most morticians a cold chill. One of us (F. L. D.) has devised a core drill fitted to a brace (figure 1).* The center drill is placed in the sella turcica and is directed in the midline and in the plane of the facial notches of the mandible (figure 2). The core (figure 3) brings out the sphenoids, the posterior ethmoids and part of the nasal cavities and turbinates, generally shears the mesial walls of the maxillaries and leaves the pharynx, tongue and tonsils exposed. By making a sagittal section of the core, one will have had a complete exposure of all of the paranasal sinuses save the frontals and remaining ethmoids which may be easily opened through the orbital and ethmoid plates with a chisel.

Current conceptions of chronic sinus

*Arrangements have been made with V. Mueller and Company of Chicago to supply this core drill.

pathology are based largely on material removed at operation. The process is considered to be an inflammation with epithelial hyperplasia. Eggston[6] gives the following histopathological classification: (1) hypertrophic and polypoid, (2) atrophic or fibrotic, (3) mixed types. A better classification is that of Runge[7] who considers chronic inflammation of the sinuses as chronic catarrhal and chronic purulent, both hyperplastic. The latter he sub-divides into (1) an edematous or hypertrophic type, (2) a granulomatous or papillomatous type, and (3) a fibrotic type. It would seem that the various types described are merely different reaction patterns in the same pathological process. The multiplicity of pictures observed are conditioned by varying tissue responses to irritants, by the number, character and duration of acute infectious insults and by varying degrees of swellings and unswellings

FIG. 1. Core drill. Two inches in diameter as used for average and large adults.

which may profoundly change the reaction patterns in relatively brief intervals of time. One may obtain sections from a single sinus which run all the histopathological patterns described by various authors as different "types" of hyperplastic disease. (Figures 4, 5, 6, 7). One of the most striking variations is in the water content. Wherry[8] sees in tissue hydration a condition necessary for bacteria to invade the emulsion colloids of the body. In the abnormal variations in the water content of the mucous membranes may lie the tendency in certain inviduals to repeated upper respiratory infections. In this connection it is interesting to note that most hay fever patients ultimately develop a chronic sinusitis. Massive hydration and dehydration of the sinus mucosa accounts for the startling variations observed in allergic individuals by Proetz[9] and others. Hydration factors and the high variability of the tissue reactions seen bring up the question of whether a pathological classification made on the basis of reversibility might not be more useful. As clinicians we

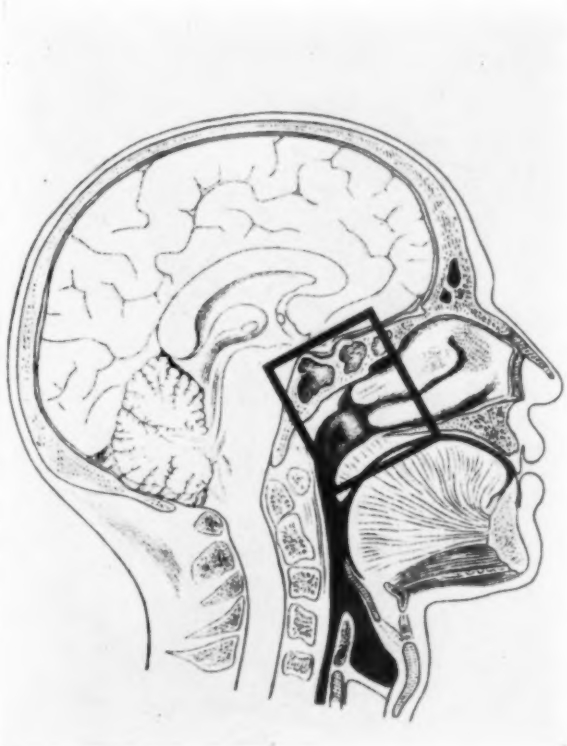

FIG. 2. Midsagittal schematic section of head showing orientation of coredrill in use and portion included in core. The core includes sphenoids and posterior ethmoid sinuses, the posterior nasopharynx, fossae of Rosenmüller, posterior portions of turbinates and portions of the soft and hard palate. On removing the core the maxillary sinuses, tonsils, tongue, pharynx, and back teeth are accessible.

are primarily interested in whether changes observed are fixed or relatively transient; whether changes revealed by roentgenograms with or without lipiodol or by endoscopy are reversible or irreversible; and what are the corresponding histopathological patterns. Such knowledge will ultimately determine the indications for conservative or radical methods of treatment.* In the problems of tissue hydration are involved the baffling interrelationships of asthma and upper respiratory infections. There is evidence that the answer to many of the bacterial asthmas will be found in chronic infections of the sinus mucosae.

It is unfortunate that we are forced to resort to pure morphological methods to identify bacteria in mucous membranes. Although rigorous precautions be taken to insure a sterile technic, deductions from cultures obtained from sinus membranes are open to the criticism of contamination. We have repeatedly found bodies in the deeper areas of tissues stained by the Gram method which in our opinion are diplococci (figure 8). Similar findings

*Correlation of results obtained by radical operation with the type of inflammatory reaction present in the tissues submitted has shown that favorable results are more likely the deeper the tissue infiltration; where the inflammatory reactions are superficial the process is quite likely to be a pansinusitis and belong to the allergic type. Fibrotic membranes are commonly associated with suppuration and are irreversible.

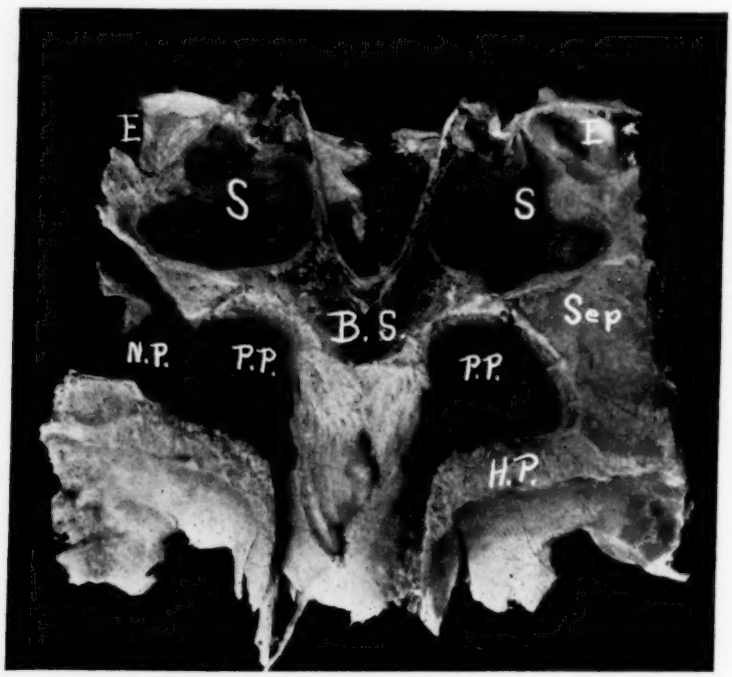

FIG. 3. Core sawed open by sagittal cut. S = sphenoid. E = ethmoid. B.S. = base of sphenoid. P.P. = posterior pharynx. Sep. = septum. H.P. = hard palate. N.P. = nasopharynx.

have been reported by others*.[10, 11, 12]

If pathogenic bacteria reside in diseased sinus tissues and find conditions more suitable to their growth in the deeper layers, obviously only those operative methods which accomplish a removal of the entire membrane should be considered in testing the focal infection theory as it pertains to chronic sinusitis. In analyzing our material the percentage of desirable clinical results was greater in those cases in which the material removed formed "casts" of the sinuses suitable for photographic reproduction (figure 9). When the specimens were badly torn or in fragments (figure 10) the follow-up showed a higher percentage of therapeutic failures. In other words, results were roughly proportionate to the degree in which an *en masse* removal of the diseased sinus mucosa was approached.

Chronic hyperplastic sinusitis as a

*Cultures made with aseptic precautions from the mucosa of an asthmatic showed an organism in pure culture similar to those demonstrated later in the tissues. The cutaneous reaction to this organism was very sharp. The patient became immediately free from asthma following exenteration of his maxillary sinuses. Three months later a cutaneous reaction to the vaccine could not be obtained.

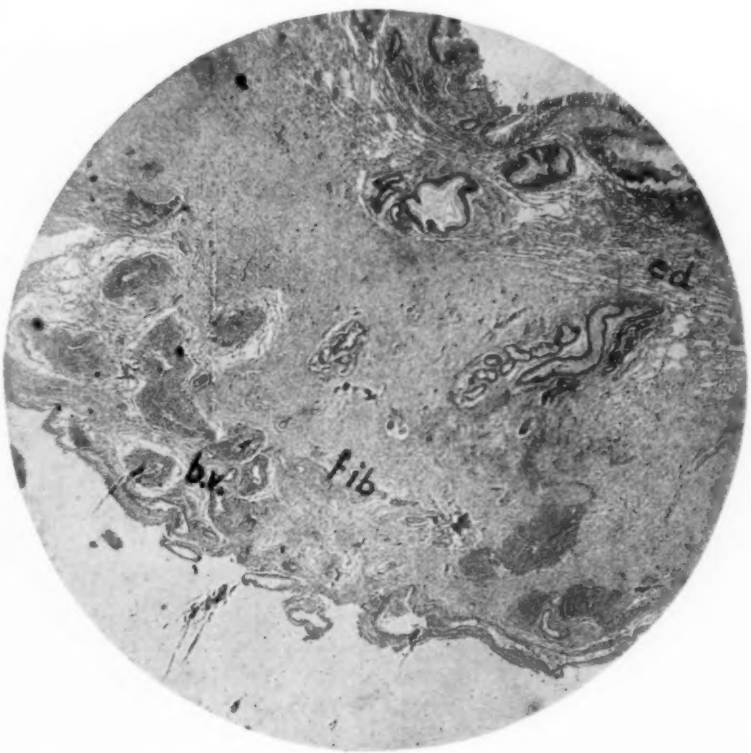

FIG. 4. Case no. V, V. H. Low power of portion of maxillary sinus membrane illustrating the variety of pathological processes which may be present in a single field. ed. = edema and hydrops. fib. = fibrotic deeper layers. b.v. = markedly thickened bloodvessels.

focus of infection has not been generally accepted. Some maintain that chronic (suppurative) sinusitis rarely if ever acts as a focus of infection;[13] others that it is not an uncommon source of systemic disease.[14] A partial explanation of such wide variance in opinion may well lie in the technic employed in treatment. Drainage of a sinus merely gives a sick membrane a better chance to get well by helping it to rid itself of its secretions. Drainage in no way eliminates the focus. Washing with antiseptic solutions should have about the same effect on a chronically infected mucous membrane as the same type of treatment might have on chronically infected tonsils. Currettement of the mucosa should yield approximately the same results as currettement of tonsils, and it has been amply demonstrated that incompletely removed tonsils merely become greater liabilities from a focal infection standpoint. The validity of clinical experiments to determine the rôle of chronic sinusitis as a focus of infection hinges on a technic which will approach a bacterial excision of the focus. To strip intact diseased mucous membranes of varying degrees of friability from the walls of bony cavities of low accessibility requires the perfection of a surgical technic totally different from any hith-

FIG. 5. Case no. V, V. H. Higher power showing the hydrops and epithelial proliferation together with the inflammatory infiltration.

erto known. Bacteriological, immunological, and pathological studies with animal inoculations will be helpful, but unless unanticipated methods be developed the solution of the problem of sinus infection in systemic disease in the final analysis will come from a statistical treatment of large series of clinical experiments, *the validity of which rests on rigorous diagnostic studies and a surgical technic which accomplishes an en masse excision of infected tissue with minimum trauma and without post-operative hemorrhage.*

Results obtained in divers conditions such as chronic bronchitis, bronchiectasis, asthma, chronic arthritis, fag, nephritis, myocarditis, chronic heart muscle insufficiency, low grade toxic states, etc., in selected cases, have convinced us of the focal possibilities of sinus disease. Exenteration has been advised in patients whose troubles have been of some standing, who have undergone long and various treatments, and whose sufferings have been such as to make them willing to submit to any treatment that offered even a remote chance of success. We have never advised exenteration in troubles of short duration, or where there seemed any likelihood of improvement by less radical methods. Care has been taken to eliminate dento-alveolar sources of chronic sinusitis. Removal of affected teeth and diseased bone by

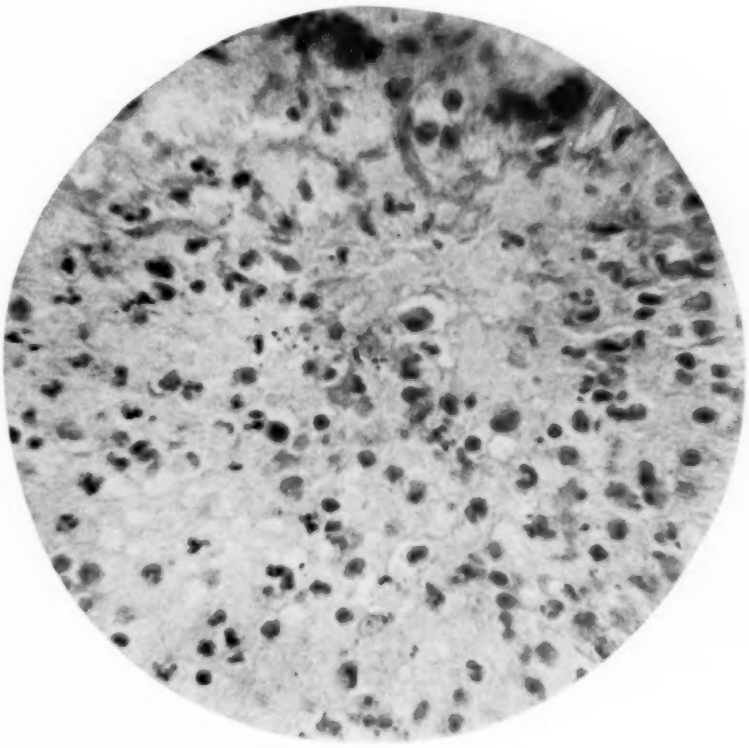

FIG. 6. Higher power of figure 5.

alveolectomy* [15, 16] has been advised, letting the sinus mucosa alone if there seemed to be any reasonable chance of recovery from removal of the adjacent diseased tissue. Partial excision of the mucous membrane has been tried in a few instances with questionable results.

What we have said has been based largely on our experiences with chronic disease of the maxillary sinuses. The more nearly the condition has been confined to the maxillaries the better have been the results. The maxillaries are more accessible from both diagnostic and surgical standpoints. A larger mass of infected tissue can be com-

*This operation, first devised by W. L. Shearer for cosmetic purposes, as developed and used by him is a highly satisfactory method for the removal of pathological conditions of the mouth. The mucoperiosteum is deflected from the alveolar processes and the teeth removed; all pathological tissues are exposed and removed "under the eye"; the bony tissues are trimmed and smoothed, and the muco-periosteum trimmed and sutured. Healing is by primary intention. The "reactions" so common to other methods for the removal of teeth and mouth lesions are practically unknown. This method, when correctly applied, permits the removal of all lesions of the mouth at one sitting without fear of dangerous reaction. Twenty years experience with this technic has convinced us that in proper hands it is the method of choice for removal of dento-alveolar foci of infection.

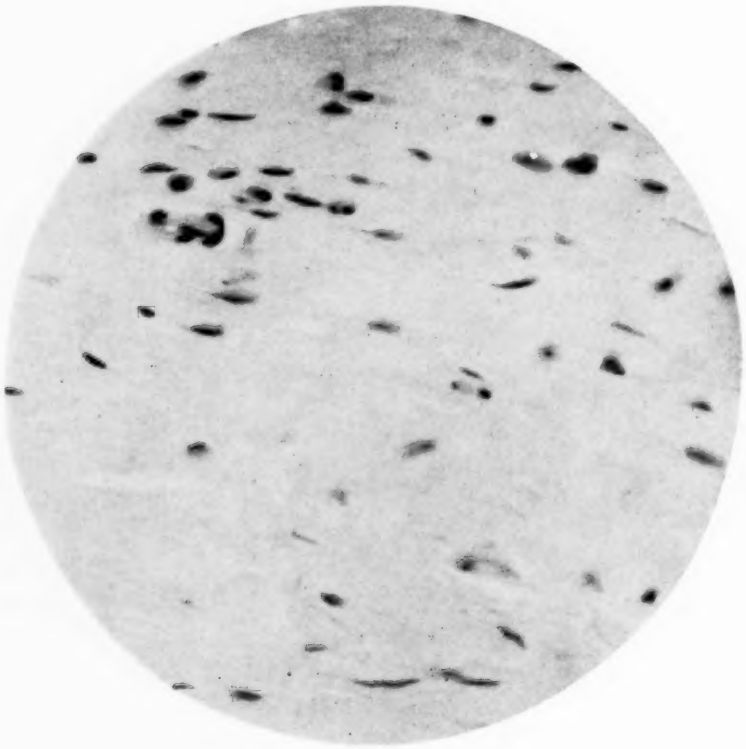

FIG. 7. Fibrosis in deeper layers.

pletely removed with less technical difficulty—a quantitative advantage. Satisfactory improvement occasionally follows maxillary exenteration in the face of involvement of the sphenoids and ethmoidal labyrinths—also a quantitative effect. We have made no studies of bone involvement described in connection with chronic sinusitis. Autopsy studies of this problem would seem pertinent.

The following brief abstracts from case records illustrate the results that may be obtained in favorable cases, and in which it seems reasonable to assume that the exenteration of diseased sinus mucosae has been a determining factor in the patient's improvement or recovery. Failures have been present, especially in pansinusitis in patients in whom we have had reason to suspect that the exenteration has been incomplete, or when the systemic conditions seemed to have become fixed, when other variables have been present, or the focal nature of the trouble questionable.

Case Report

Case No. 1: E. S. L., single, 19, entered the hospital March 25, 1925, with a diagnosis of acute rheumatic fever and acute endocarditis. She gave a history of yearly recurrent attacks of acute rheumatic fever from the age of 5 until her tonsils were removed at 13. She was known to have a

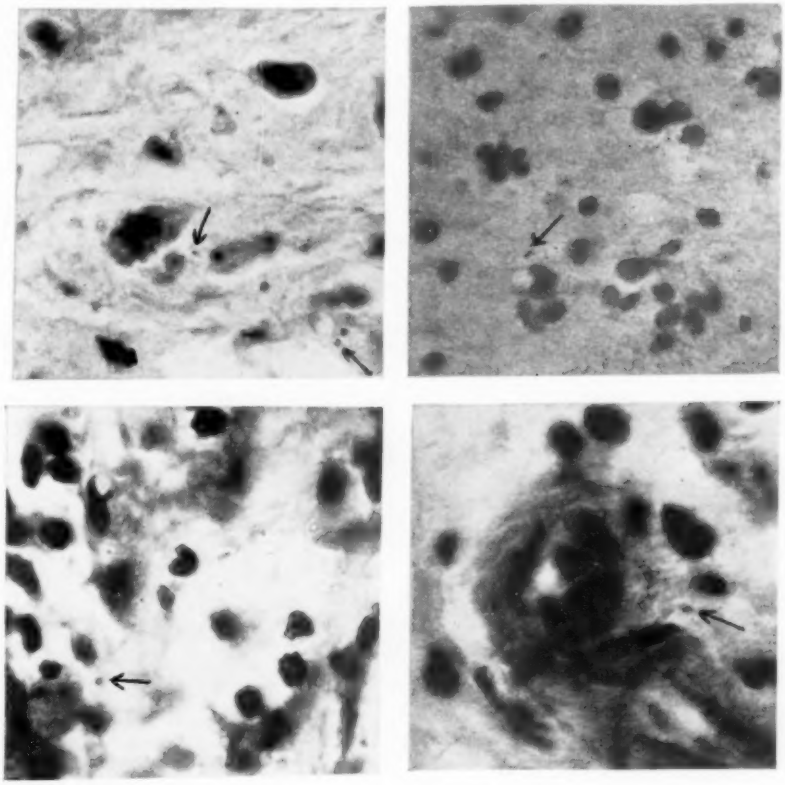

Fig. 8. Diplococci indicated by arrows. Gram-Weigert stain.

FIG. 9. Case no. VII, M. C. En masse exenteration of both maxillary sinus membranes. Coronal section. The material has been removed in one piece and the membrane is complete except for the usual tearing along the medial wall near the ostium.

FIG. 10. Exenteration of left maxillary sinus membrane by usual method. Such material makes any opinion as to the completeness of the operation hazardous and suggests at least considerable trauma.

damaged heart but her health had been reasonably good from that time until three weeks prior to her admission, when she contracted a cold, which was followed by a low grade fever. There was a profuse nasal discharge and she ached all over. Her knees became red, swollen and very painful, and she grew short of breath.

The physical examination showed a pale, young woman, orthopneic with acute rheumatic manifestations. The heart action was rapid. The apex was in the fifth interspace, 9 cm. from the median line. The heart was 12 cm. broad at the fourth interspace. From the heart findings a diagnosis of lesions at both mitral and aortic valves and of acute fibrinous pericarditis was made (the friction rub disappeared in 72 hours).

The urine examination was negative. The blood count showed a hemoglobin of 80; red blood cells, 4,200,000; leucocytes, 12,700. The Wassermann test was negative.

A remittant fever continued uninterruptedly for three weeks and on account of the history, rhinological and roentgenographic findings an attack upon the sinuses was decided upon in spite of the desperate condition of the patient.

Exenteration of the infected ethmoids and intranasal drainage of the maxillaries and sphenoids on both sides were done. Pus was found in both maxillary sinuses. Five days after the operation the temperature reached and held the base line. Convalescence was uneventful.

Comment. From the history, findings and clinical course one would have been justified in assuming an acute rheumatic or subacute bacterial endocarditis affecting previously damaged valves. Because there was a history of onset with an acute upper respiratory infection and clouding of the maxillary sinuses we decided to consider the sinusitis as a source of infection with or without a complicating acute or subacute endocarditis. On drainage of the infected sinuses, a condition presumably of a precarious outlook, became relatively benign. Serious re-infection, if any, of the endocardium had not occurred. The sinusitis was responsible for the febrile course. We have seen several similar cases and have come to consider the diagnosis of acute infectious endocarditis, even in the presence of obvious heart findings, as hazardous without excluding acute or subacute paranasal sinusitis. In the case under consideration we thought the sinusitis was of the acute suppurative type and the changes probably reversible. The patient has had no illnesses since, and would be considered a perfect physical specimen were it not for the valvular heart lesions. A Waters plate at the present time, however, shows hyperplastic membranes which were best removed as a preventive measure.

Case No. II. D. P., a young, married woman, age 23, was brought to the hospital July 27, 1929, with asthma, which had completely incapacitated her for the past six months. There was a history of repeated respiratory infections: "pneumonia" at 4, 17, and at 19 when she was sick six weeks. The first attack of asthma had occurred in August, 1926. She had changed climate three times; elimination diets and protein tests had failed to reveal any allergic factors. Both maxillary sinuses were radiopaque. A clinical survey revealed nothing of significance except the signs of a chronic bronchitis with emphysema and a leucocyte count of 10,300.

Middle turbinectomy and radical exenterations of the mucous membrane of both maxillary sinuses were done. Both antra were filled with polypi and thick, foul smelling pus. The mucous membranes were decidedly fibrotic in type with marked perivascular changes. The epithelium was not normal but in places columnar. A large share of the specimen was made of dense connective tissue with long, thin nuclei. Diplococci were present.

A report on Jan. 30, 1932, states: "I am in better health than since childhood. I have had no bad attacks of asthma. Once in a while if I run or exercise too hard in the cold I will "stuff up" for about 10 or 15 minutes. At times when out in the cold or just before a storm my face hurts and I have pain between the eyes and in the cheeks" (probably ethmoid disease).

Comment. This is a fairly well controlled case of severe intrinsic, incapacitating asthma, in which prompt and complete relief followed a radical exenteration of the diseased mucosae of both maxillaries. Asthma patients should be studied from the standpoint of sinus infection either as a causative or a complicating factor. Severe cases, obviously intrinsic, with hyperplastic sinusitis should be given the benefit of the experiment of a complete exenteration, especially if the disease seems to be confined largely to the maxillaries. After all, as Rackemann says, "It is infections that play havoc with our patients" which holds especially true of asthma.

Case No. III. Mrs. A. A., age 70, had suffered from asthma for 20 years. During the past two years the asthma had increased in severity until it had become incapacitating and life threatening on account of impending heart failure. A careful history disclosed the fact that the onset of the asthma twenty years ago had been preceded by *extensive dental work involving devitalization of many of her upper teeth.* Changes of climate and various dietetic, hygienic, and medicinal regimes had been instituted without benefit. During the past two years her asthma had been practically constant and her condition had been made endurable only by the use of several hypodermics of adrenalin daily.

The physical examination showed a poorly nourished, elderly woman, orthopneic and cyanotic. The general physical examination revealed nothing further of marked import except a somewhat enlarged heart with a slight systolic blow at the apex, various sized dry râles over the entire chest, slightly enlarged liver, and edema of the legs. Rhinological examination yielded nothing of significance except tumefaction of the left inferior turbinate. Radiograms in the Waters position showed moderately increased density in the floor of the maxillary sinuses, especially the left. There was marked dento-alveolar disease throughout the upper jaw with obvious involvement of the floor of the left maxillary, and possible involvement of the right.

Because the patient had suffered from asthma wherever she had lived and whatever she did, because diets had been tried and sensitization tests run by others, and because the onset of the asthma so closely followed devitalization of teeth twenty years ago, and because of such definite evidence of dento-alveolar and sinus disease on the left side, an alveolectomy with removal of the dento-alveolar disease and a Caldwell-Luc operation were done on the left side Feb. 12, 1930. On account of the critical condition of the patient no work was done on the right. Twenty-four hours after the operation the patient had her last hypodermic of epinephrin for that attack which had lasted unabated for six months.

The patient is reported (March 20, 1932) as being relatively free from asthma although there has been some wheezing and shortness of breath on exertion.

Comment. The past two years have been relatively comfortable for this patient. Contrary to advice the patient did not return to us for mouth work on the opposite side, but merely had the teeth extracted. This patient illustrates the important relationship of dento-alveolar disease to chronic sinusitis and to asthma via the sinuses.

Case No. IV. H. M., farmer, aged 70, came under observation June 23, 1930. There was nothing of significance in the past or family history. He stated that he had been quite well until three or four years ago when he noticed severe spells of coughing and shortness of breath associated with choking

spells nocturnal in type. During these times he had to be propped up in bed, for whenever he lay down he began to cough and choke. He said he had never had asthma and that he felt pretty well in the daytime but his nights were bad and dyspnea had been present on slightest exertion. There were no other symptoms of significance.

Examination showed a poorly nourished, elderly man, slightly cyanotic who choked up and coughed when he lay down. The following significant things were noted on the general examination: marked dento-alveolar infection; a moderately enlarged heart; pulse, 72; systolic blood pressure, 112; diastolic, 82; a systolic blow heard all over the precordium, musical in character and well transmitted to the axilla. There was no obvious evidence of heart failure.

Films showed very extensive alveolar disease with clouding of both maxillary sinuses, the latter corroborated by lipiodol filling defects. An electro-cardiogram showed low amplitude Q-R-S in all leads; conduction time normal; T-wave upright throughout.

Diagnosis: Extensive dento-alveolar disease; chronic hyperplastic sinusitis; asthma (?); chronic myocardial insufficiency.

Under observation in the hospital the attacks of dyspnea were largely at night and partook of the type of cardiac asthma. The urine examination was negative. Hemoglobin, 9.7 gms. (56 per cent); red cells, 3,590,000; whites 15,000, 50 per cent polymorphonuclears. The Wassermann test was negative.

Double alveolectomy with exenteration of both maxillary sinuses produced a remarkable change in the patient's symptomatology.

Patient is reported (March 28, 1931) by his local physician as very active and reasonably well for a septuagenarian.

Case No. V. V. H., age 16, consulted us on Jan. 3, 1930, for heart trouble. There was nothing of significance in the family or in the past history except tonsillectomy and adenoidectomy which were performed six years ago for repeated attacks of tonsillitis; there has been more or less constant catarrhal trouble for years; he has been subject to colds which have kept him out of school for weeks at a time.

Two years ago the patient had "an upper respiratory infection with bronchitis which "left his heart weak". Ever since that time he has been troubled with rapid heart action and palpitation. If he over-exercises his heart beats fast and he has a feeling of "being all in". He gets short of breath on going up hill. He also has pain and stiffness in the back at times. Recently every time he "gets bronchitis" his "heart is bad", and he has to stay in bed for weeks at a time.

The physical examination showed a well developed, well nourished lad. There was a pharyngeal lymphangitis and some enlargement of the posterior cervical glands. The tonsils were out and there was no evidence of mouth infection. The pulse rate lying was 88; sitting, 104; standing, 120. After 50 hops the pulse went to 142. One minute later it was 122 and five minutes after the 50 hops it was 106. There was no increase in the size of the heart and the sounds were normal. The systolic pressure was 135; diastolic, 85; temperature, 98.8°. There was no evidence of hyperthyroidism and the basal metabolic rate was —8. The physical examination was otherwise negative.

The urine examination was negative. The blood count was normal and the Wassermann test was negative. The electrocardiogram showed a rate of 90, R-wave upright in all leads, R-wave slurred in all leads, T-wave slightly diphasic in leads II and III. Sinus tachycardia, sinus arrhythmia.

Clinical diagnosis: Myocarditis, probably having origin in sinus infection.

A radiogram in the Waters position showed a large filling defect in the floor of the left maxillary sinus and clouding of the left ethmoids, graded +3. A rhinological examination showed the septum deviated to the right; considerable hypertrophy of the middle turbinates, with swelling and edema of their posterior tips.

Operation. Bilateral middle turbinectomy, ethmoidectomy, radical left maxillary with *en masse* removal of mucous membrane, exploration of right maxillary.

Microscopically the membrane was of the chronic diffuse inflammatory type, the thickening of the membrane being due to fibrosis and not to edema. The epithelium appeared almost normal in many places. In other places the cilia were absent. Conclusion:

Chronic fibrous sinusitis, irreversible with little possibility of recovery by other than radical measures.

Comment. Rapid improvement followed the operative attack. At the end of two years the patient was well. He has had only occasional colds and no cardiac symptoms. The rapid cessation of symptoms and the resumption of growth and development on the part of this boy following the radical removal of the sinus infection has been striking. It is reasonable to assume that we were dealing with myocardial damage, either toxic, or from myocarditis due to actual bacterial invasion of the heart muscle, and that the focus was in the sinuses.

Case No. VI. F.R.H., farmer, aged 51, consulted us Jan. 23, 1930, because of "fag". The patient had enjoyed good health until three years prior when he began to have attacks characterized by weakness, loss of appetite, soreness across lower abdomen, slight fever, a yellow sallow color anl unaccountable sweating. During these attacks, which were often precipitated by changes in weather, he ached all over and there was some chilling. There has been no nausea, vomiting, excessive gas or constipation, nor mucus in the stools. These attacks have been growing in frequency and have been gradually incapacitating him. There was no history of tonsillitis or repeated upper respiratory infections. The past and family histories were of no importance and there was little history of catarrh.

The patient was a well developed, middle aged man, with a dirty, sallow, subicteric hue. He seemed exhausted. His skin was wet. The tonsils were adherent, the anterior pillars red, and pus could be expressed from the left one. There was no particular enlargement of the submaxillary glands. There was a lateral pharyngeal lymphangitis, especially on the left, but no enlargement of the posterior cervical lymphatic glands or of the thyroid. The examinations of the heart, lungs, abdomen, rectum and nervous system were negative.

A Waters plate showed the right maxillary sinus fairly clear, left clouded (graded +3), frontals and ethmoids apparently negative. A rhinological examination showed mucopurulent secretion in the left nares and swelling of the left middle turbinate. Films of the teeth showed dento-alveolar disease and an unerupted molar on the right side, residual pathology and a partly erupted molar on the left, and probable involvement of the floor of both maxillary sinuses, especially left.

Diagnosis. Focal infection with two obvious foci, tonsils and dento-alveolar disease with a left chronic hyperplastic maxillary sinusitis secondary to periapical disease.

The tonsils were removed, Jan. 7, 1930. No improvement followed. Bilateral alveolectomy with resection of polypoid masses from floor of left maxillary sinus was done on Feb. 20, 1930. The mucosa of the right maxillary sinus appeared approximately normal and was not resected. An x-ray film in the Waters position showed a normal left maxillary sinus shadow on April 9, 1930. During the early summer the patient felt some better but his improvement was not satisfactory. There was a return, however, of the old trouble with loss of weight, sweating, and increased fatigability in September, 1930. In December, 1930, he had a severe attack with headache, aching all over and fever up to 101°. Recently he has had a cough. There has been no pain in head, but patient feels as if he were "taking cold" with chilling at night; there has been a great deal of nasal discharge.

Rhinological examination (Jan. 7, 1931) showed very definite evidences of sinusitis. A Waters' plate showed the right antrum with opacity graded +1; left, +2. Lipiodol showed considerable thickening of mucosa of right maxillary sinus and a marked filling defect of the left. Stereoscopic plates of the chest revealed nothing but the peribronchial infiltration usually associated with a chronic sinusitis. Intravenous cholecystography showed a normally functioning gallbladder.

Diagnosis. Chronic hyperplastic sinusitis of both sides, recurrent on left. On Jan. 14, 1931, bilateral Caldwell-Luc operations with *en masse* removal of mucosae of both

maxillary sinuses were done. The left maxillary sinus was half filled with thickened mucous membrane with polypoid hyperplasia. A pocket of pus was found in the mucous membrane in the anterior-inferior portion. The right antrum showed the same type of membrane as the left but with pus filling the entire cavity.

The patient reported well on March 23, 1931.

Comment. This patient presented an obscure diagnostic problem, infectious in origin. After removal of the tonsils without improvement, bilateral alveolectomy with removal of polypoid masses from the left maxillary brought some improvement with a normal left maxillary sinus shadow. Recurrence of the chronic hyperplastic sinusitis with polypoid masses in the left and with suppuration on the right necessitated radical procedures. A satisfactory recovery followed exenteration of both maxillary sinuses.

Case No. VII. M. C., widow, age 46, consulted us on June 19, 1930. There was nothing of significance in the past or family histories.

Present Illness. The patient had enjoyed excellent health until December, 1928, when she had influenza and was in bed five days. Her nose was stopped up; she had fever and severe headache. She had had some catarrhal trouble previously but it became much worse afterwards. Since then she has never been well. A tonsillectomy was performed, and three abscessed teeth were removed in July, 1929. The only result was a rapid increase in her weakness. In September, 1929, she was taken with terrific pains in the stomach and bowels, and was unable to sleep or eat, for which she was hospitalized. Since then there have been more or less abdominal distress and insomnia. She has had night sweats. She has been constipated and forced to take almost daily cathartics. Her chief complaints were extreme weakness, pain and distress in the abdomen, headache, especially on the right side, with a sensation of pressure and a feeling of fullness and ringing in the ears. She has been hospitalized three times since the onset of her trouble, undergoing a rest cure and treatment of 12 weeks' duration for mucous colitis.

The physical examination showed a poorly nourished, tired appearing woman with a woe-begone, neurasthenic facies. The abdomen was diffusely tender with sharply localized tenderness without rigidity in the right lower quadrant. Otherwise the physical examination revealed little of importance. The urine examination was negative. The blood count was:—hemoglobin, 12.3 gms. (Newcomer); red blood cells, 3,980,000; white cells, 6,400; polymorphonuclears, 60 per cent; mononuclears, 40 per cent. The blood Wassermann test was negative. The gastro-enterological examination was negative except that the appendix did not fill with barium; the right lower quadrant of the abdomen was tender, and the colon was spastic. A rhinological examination showed no evidence of paranasal sinus trouble but a Waters' plate revealed changes in density which were confirmed by lipiodol.

On account of the possibility of a chronic appendicitis the patient was hospitalized for observation and placed on a smooth-anticonstipation regime for three weeks with little improvement in the abdominal symptoms. Radical excision of the mucosa of both maxillary sinuses was performed on July 8, 1930, (figure 9) and was followed in four months by a normal state of health. Both antra were practically filled with polypi and thickened mucous membrane; multiple abscesses containing thick yellow pus were found in the mucosae.

The patient reported herself well on September 17, 1931.

Comment. This patient is of interest from several standpoints: (1) A text book case of (neuro) asthenia may be associated with a sinus infection. (2) Typical mucous colitis with abdominal pain, spastic intestine, etc., may be completely relieved following removal of a sinus focus of infection. (3) The diagnosis of this infection

was made entirely on the clinical record with the help of roentgenograms. Examinations by two rhinologists without films brought back a report of "no material evidence for paranasal sinus pathology".

Summary

1. A brief statement of sinusitis as a general medical problem has been attempted.

2. Three postulates for a valid clinical answer to the question of chronic sinusitis as a source of systemic disease may be layed down, viz:—(1) rigorous diagnostic surveys, (2) a technic which accomplishes a bacterial excision of the infected tissues, and (3) statistical studies of series of cases which satisfy the first two postulates.

3. A core drill, which should help in promoting routine post-mortem examination of the sinuses has been described.

4. Abstracts from the clinical records of a few illustrative cases, with comments, have been presented.

We wish to express our appreciation to Drs. J. B. Potts and W. A. Cassidy, rhinologists, and to Drs. W. L. Shearer and R. R. Ralston, oral surgeons, for their helpful cooperation in this work.

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The Local and Constitutional Pathology of Bronchial Asthma*†

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Ann Arbor, Michigan.

Grimm,[1] in 1925, found but thirty cases of bronchial asthma with autopsy findings and microscopic studies. Since that time, nine additional cases have been recorded: by Rackemann[2] (one), Kountz and Alexander[3] (three), Dehner[4] (two), Steinberg and Figley[5] (two), and Wright[6] (one). Of this total number of thirty-nine cases, careful studies have shown[2] that many of the cases earlier reported were not true bronchial asthma, while in not more than twelve cases can death be said to have resulted directly from asthmatic paroxysms. Huber and Koessler,[7] in their monograph upon the subject in 1922, presented only four cases from the literature (amongst twenty-one), and one of their own series (number 2), in which death resulted from a seizure of bronchial asthma. The remaining fatal cases are gathered from the above authors, Kountz and Alexander having the largest series of three deaths, although Rackemann reports having attended five patients in whom death was apparently due solely to an asthmatic seizure, but autopsy was not performed.

Collected from 3,690 autopsies at the Hospital of the University of Michigan since 1896, is the following series of eight cases, in five of which death can be laid to asphyxia or cardiac failure during, or immediately following a paroxysm of bronchial asthma.

In this study, attention has been paid particularly to the pathology of the individual structural layers and units of the bronchi and peribronchial tissue. For two reasons no attempt has been made to determine absolute measurements of bronchial wall thickness: (1) Many apparent fallacies render this procedure of uncertain value. The most important source of error is the wide variation in the activity of individual units of the bronchial exudative system—mucous epithelium, glands, blood vessels and capillaries. Furthermore, it is evidently quite impossible to obtain a comparable series of cross sections of bronchi from any two individuals, dependent as they are for accuracy upon the distance from bifurcations (cartilage-plaque thickness), individual variations in structure, and the varying states in which the mucosal, submucosal, and muscular layers may be found postmortem, as well as upon technical artefacts. (2) In spite of these difficulties, Huber and Koessler,[7] and later, Kountz and Alexander,[3]

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†Submitted for publication February 15, 1931.

were able to show quite definitely, by painstaking measurements of the bronchi of asthmatics and non-asthmatics, a thickening of the bronchial walls as a whole at certain levels, and of the individual layers, in the asthmatic individual. The uniformity of results obtained by these investigators makes certain the fact that the bronchial thickening seen grossly and microscopically, is not only apparent but real. For present purposes, then, the bronchi are divided relatively into those of small, intermediate, and large orders, those of intermediate size ranging from 2 to 5 mm. in outside diameter. They were studied with reference to their respective layers, recognizing the epithelial mucosa (with goblet cells), basement membrane (upon which the former rests), subepithelial layer, musculature, glands, fibrocartilaginous layer, variable lymphoid tissue, and the vascular and nerve supply.

It is proposed not only to correlate the clinical and pathological findings in this series, but to view such results in the light of the theories of etiology in vogue at the moment. In particular, the proof for that type of asthma known as "bacterial" will be questioned. An effort will be made to review the anatomic findings in these cases with the hope of finding indications of some basic factors in the predisposition (if such there be) of the individual to allergic phenomena in general.

Case Reports

Case I. (Path. No. A-I-AI) O.S., a male aged 43 years, was first a patient in the University Hospital in April, 1930, and subsequently returned for further treatment towards the end of June of that year. For five years he had suffered from attacks of paroxysmal dyspnea, increasing in frequency and severity, and accompanied by a cough which at times was productive of a small amount of yellowish sputum. The dyspnea was inspiratory in type. The relief obtained from epinephrin was inconstant. With the periodic lessening of a chronic nasal discharge would come headaches, and more frequent and severe attacks of asthma. A thirty-pound loss in weight during the preceding year and occasional malleolar edema were noted.

Clinical and laboratory studies showed evidence of pansinusitis, nasal polypi, slight leucocytosis, a blood eosinophilia of 13 per cent, and an inconstant hypertension, as well as the classical physical signs of bronchial asthma. Sensitization tests showed positive reactions for hemolytic and nonhemolytic streptococci, and micrococcus catarrhalis from stock vaccines. Sputum culture yielded a hemolytic streptococcus, *Streptococcus viridans*, and *Micrococcus catarrhalis*. From these cultures vaccines were prepared, with which positive sensitization reactions were shown to a nonhemolytic streptococcus and *Micrococcus catarrhalis*.

During his stay in the hospital the patient was observed in many asthmatic attacks. Some were so severe as to give the impression of impending death. Such attacks resisted the administration of epinephrin, atropine, nitroglycerin, morphine, and magnesium sulphate, while those of less severity responded to the use of epinephrin. The nasal polypi were removed during April. In June the autogenous vaccine was given for a short time in repeated small injections, but during this procedure the attacks became so severe that the course had to be discontinued. On several occasions it had been noticed that severe attacks of asthma had followed the administration of coal tar products. On July 1st, one-half hour after taking 0.6 gm. of aspirin, the patient suffered a severe attack of asthma, in the midst of which death occurred, evidently from respiratory failure. Artificial respiration was of no avail although the heart sounds were audible for twenty-five minutes after the cessation of respirations.

Autopsy was performed nine hours post mortem. The body was that of a well developed, emaciated white male, 162 cm. in

length. The thorax was not remarkable on external examination. Upon removal of the sternum, the lungs ballooned out into the incision in close approximation. A marked dilatation of the right heart was noted. The right ventricular wall measured 8 mm. in thickness, of which one-fourth was composed of fat. The tricuspid valve admitted three fingers, and the pulmonary valve two. Both valves appeared normal. The left ventricular wall measured 20 mm. in thickness. The mitral and aortic valve orifices were of normal size. The mitral valve, near the attachment of the chordae tendineae, presented indurated, nodular thickenings, and adjacent endocardial sclerosis. No gross areas of fibrosis were noted. The heart as a whole measured 14 by 10 by 5 cm., and weighed 280 gms. The left lung measured 25 by 17 by 7 cm., and weighed 300 gms., while the right lung was 23 by 19 by 8 cm., and weighed 310 gms.

The lungs were extremely voluminous. Both apices presented rather firm adhesions. The lungs were fully air-containing throughout, of uniform spongy consistency. They cut with markedly increased resistance. Both parietal and cut section surfaces were mottled slate gray in color, with some reddish coloration in both lower lobes posteriorly. The large bronchi gaped widely, with evident thickening of their walls. The smaller bronchi contained mucous plugs resembling tenacious jelly, and adherent in many places to the bronchial walls. The trachea and main bronchi showed redness and swelling of the mucosa, with slight amounts of mucinous exudate.

Further gross examination revealed no notable findings. Blood culture at autopsy gave a growth of *B. pyocyaneus* and *B. coli*. The Kahn procedures, both diagnostic and presumptive, were negative.

Microscopic Examination. Localized thickenings of the leptomeninges were noted with one area of active infiltration. Most notable in the heart was a patchy fibrosis of the myocardium, with atrophy and hypertrophy of the heart muscle. Endocardial sclerosis of long standing, and advanced atherosclerosis of the coronaries were additional features. Small latent syphilitic lesions were present in the aorta.

In general, the lungs showed a well marked emphysema, with numerous small patches of fibrosis. Areas of chronic passive congestion were noted. The terminal bronchioles and smaller bronchi were dilated, and some of them contained plugs of laminated mucus. Even the small bronchioles showed a hyalinization of the basement membrane. The changes in the bronchi of intermediate size, however, were more marked. A majority of these showed laminated and stratified mucus filling the lumina and constituting Curschmann's spirals. The lumina were somewhat dilated, and showed frequent small saccular extensions, some of which were produced by the widening of the mouths of mucous glands. The bronchi of this order also showed marked cellular infiltration of the wall which was characteristically eosinophilic, and which in many areas pervaded the muscle. There was only a moderate degree of hypertrophy of the muscular layer in the bronchi, but a very distinctly hyaline basement membrane. The large bronchi showed changes practically of the same character as those of intermediate size. The hyaline basement membrane was wide and prominent. The eosinophilic infiltration extended to the cartilages, and in some instances occurred in the connective tissue on the parenchymal side of the cartilage plates. There was a chronic bronchitis.

The bronchial nodes showed lymphoid hyperplasia with lymphoid exhaustion. The thyroid gland was deficient in colloid, with microscopic evidence of Graves' constitution. In accord with the persistent hyperplastic thymus, the adrenals were hypoplastic, and all lymph nodes hyperplastic with exhaustion of the germinal centers. In the pancreas were seen areas of interstitial pancreatitis. Atrophic gastroenterocolitis, diffuse toxic fatty infiltration of the liver, and an early arteriosclerotic nephropathy were the only additional noteworthy findings.

Case Summary. A 43-year-old male who had "bacterial" asthma for five years, treated with autogenous vaccines, became so much worse under their use that they had to be discontinued. Already known as being hyper-

sensitive to coal-tar products, he died in a paroxysm of asthma following the ingestion of a therapeutic dose of aspirin. The significant local pathological findings were: (1) Hyalinization of a thickened basement membrane throughout; (2) most marked pathology in the bronchi of intermediate size; (3) occlusion of lumina by exudate; (4) eosinophilic infiltration; (5) sacculations of the bronchi; (6) moderate hypertrophy of the muscular layer.

Case II. (Path. No. A-38-AI) S. T., 75 years of age, was admitted to the Department of Internal Medicine in the University Hospital on September 3, 1930, and expired less than 36 hours thereafter. In the short history obtained, all details typical of attacks of bronchial asthma were related. These had their origin, evidently, eight years previously when working in a munition factory. There he inhaled large amounts of acid fumes, and soon began to suffer from asthmatic attacks. Latterly, suffering from constant orthopnea and dyspnea, with frequent daily paroxysms of asthma, he was admitted as an emergency after a tiring journey from his home in a distant part of the state. During the short time he was under observation, he passed from one asthmatic attack into another. A few hours after admission, his temperature was 102°, with a leucocytosis of 27,000. Signs in the chest were obscured by the intense asthma present. Twenty-four hours after admission, the patient became cyanosed, with marked tachypnea, and shortly thereafter lapsed into coma. In spite of appropriate measures, he died a few hours later.

Autopsy was performed 16 hours post mortem. The body was that of an asthenic white male, 183 cm. in length. Malleolar edema was present. The thorax was flat but symmetrical, the costal angle greater than a right angle. Both pleural cavities contained about 25 c.c. of clear colorless fluid. There were a few adhesions, posteriorly, of each lung to the thoracic cage. The lung borders were 1 cm. apart in the anterior mediastinum. The cardiac apex was found to be at the sixth rib in the anterior axillary line. Thymic tissue could not be seen. The heart measured 15 by 12 by 7 cm., weighed 375 gms., and appeared globular in shape, with the apex formed mainly by the left ventricle. The left ventricular wall measured 2½ cm. in thickness, without gross evidence of fibrosis. Both mitral and aortic valve orifices were of normal size, with the mitral cusps showing a slight sclerosis. The right ventricular wall averaged 6 mm. in thickness, one-sixth of which was fat. The ventricle was dilated, the musculature relaxed and flabby. There was slight relative insufficiency of the tricuspid and pulmonary valves.

The left lung measured 27 by 17 by 7 cm., and weighed 600 gms. The organ was markedly emphysematous. The lower lobe presented a sharply circumscribed area of bronchopneumonia. Throughout, the bronchi showed many mucous plugs blocking the lumina, and the bronchial walls showed very marked thickening. The right lung, weighing 820 gms., measured 26 by 21 by 6 cm., and presented essentially the same changes as its neighbor, with a slightly larger area of bronchopneumonia in the middle lobe. Here also the bronchi of intermediate size were thickened and filled with mucous plugs. The bronchial glands were enlarged and anthracotic. The spleen presented several small, calcareous nodules. Some perigastric adhesions were noted. In the right lobe of the thyroid was an adenoma of 15 mm. diameter.

Microscopic Examination. A slight myocardial atrophy and fibrosis, endocardial sclerosis and lime salt deposit in the base of the valve cusps constituted the lesions in the heart. In conformity with these changes were the aortic atherosclerosis and calcification.

In addition to an acute purulent bronchitis with acute fibrino-purulent lobular pneumonia, the lungs showed uniform emphysema and an acute exacerbation of a chronic passive congestion. The smaller bronchi were uniformly dilated, and without hypertrophy of their respective layers, or hyalinization of the basement membrane. In both the large and intermediate bronchi, but most

evident in those of large caliber, was seen hypertrophy of the musculature. In both of the latter classes of bronchi the predominant change was a thickening and hyalinization of the basement membrane. This varied in degree, and could not be said to be more prominent in one or the other class. Filling many of the larger bronchi were spirally twisted masses of mucin and fibrin (Curschmann's spirals). The bronchial outline was rendered irregular and somewhat sacculated by dilatations between the muscle bundles, and at many points this seemed to have been accomplished by taking advantage of the mouths of the mucous glands. A marked cellular infiltration about both the intermediate and larger bronchi included numerous eosinophiles. The pulmonary arteries presented a well marked proliferation of the intima, without hyaline change. There was a chronic adhesive pleuritis. In the bronchial nodes were seen, in addition to anthracosis, numbers of rather recent epithelioid tubercles, without caseation. The trachea also presented a marked hyaline change in a thickened basement membrane, under which were infiltrating large numbers of eosinophiles. There was, in addition, an active chronic purulent tracheitis.

A proliferating adenoma of the thyroid was accompanied by atrophy and increased stroma of the gland, with calcification of the thyroid arteries. In the spleen were several encapsulated calcareous tubercles. On the inferior surface of the liver the capsule was thickened, and there was a proliferation of the small bile ducts in the capsule, with brown atrophy of the parenchyma.

Case Summary. The asthmatic condition in this case apparently had its origin in exposure to acid fumes, and lasted eight years in a man aged 75 at

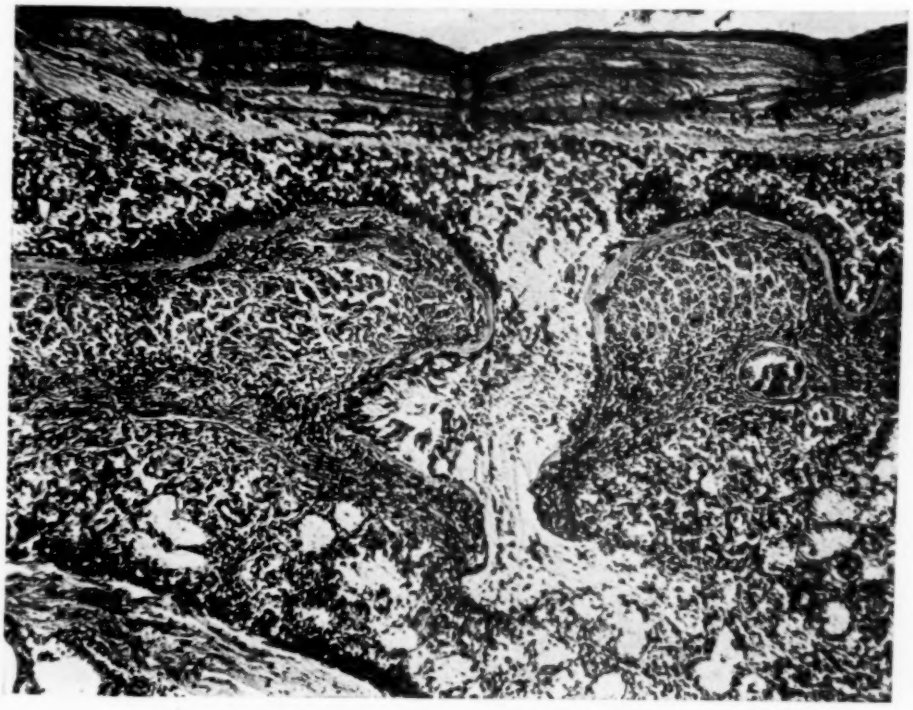

FIG. 1. Case II. Wall of large bronchus with tough mucopurulent exudate covering the mucosa. Hyaline thickening of basement membrane. Saccular dilatation of mouth of mucous gland passing between muscle bundles.

death. The terminal condition was that of extreme exhaustion brought on by repeated, successive seizures, on which was superimposed an acute fibrinopurulent lobular pneumonia. The significant findings were: (1) Hyalinization of a thickened basement membrane; (2) muscular hypertrophy most marked in the larger bronchi; (3) sacculations of the bronchi; (4) occlusion of many bronchi by exudate; (5) eosinophilic infiltration, and (6) mucous glands fairly prominent.

Case III. Z. H. (Path. No. A-122-AH), a male of 53 years of age, machinist, claimed that until eight months before his admission to the University Hospital in October, 1929, he had been without cardiorespiratory or other symptoms of ill-health. Following an attack of influenza in the spring of 1929, periodic seizures of bronchial asthma appeared, usually nocturnal. So rapidly progressive had been the course of the illness, with frequent seizures, constant dyspnea, anorexia, emaciation, asthenia, and profound general depression that in three months' time he had ceased to work and became a semi-invalid. Admitted after two weeks of almost constant dyspnea and productive cough, it was found necessary to administer adrenalin or ephedrin every three hours for the control of the constantly recurring paroxysms. In spite of such medication and the addition of morphia, the asthmatic attacks became more severe, and three days after admission death occurred during a particularly severe paroxysm, the patient having passed through six attacks during the previous twelve hours. Laboratory studies showed seven per cent blood eosinophilia and many eosinophiles in the sputum.

Autopsy. The lungs were extremely voluminous, ballooning outwards when the sternum was removed. Only a few apical adhesions were present on the right side. There were no areas of consolidation or infarction, and no evidence of a purulent process. Section revealed a striking emphysema. Many of the bronchi contained plugs of mucoid, gelatinous material. Grossly, there was no notable bronchial wall thickening. The lungs weighed 410 and 460 gms. The thymus persisted as two well-defined lobes, each one of which measured 8 by 1½ by 1 cm. The heart measured 14 by 9 by 7 cm., and weighed 335 gms. The right ventricular wall, entirely muscular, measured 1 cm. in thickness, with very marked right cardiac dilatation.

Microscopic Examination. In the heart there was a marked fatty change, subepicardial fatty infiltration, and subendocardial degenerative fatty infiltration. The hypoplastic heart muscle showed a well marked brown atrophy, and there was an endocardial sclerosis of slight degree. Except for the chronic passive congestion, emphysema, and numerous heart lesion cells, all the findings in the lungs centered about the bronchi. The terminal bronchioles were moderately dilated. In the bronchi of all degrees, but most marked in those of intermediate size, stood out a marked hyaline thickening of the basement membrane. There was, however, only a slight hypertrophy of the bronchial musculature, most evident in the bronchi of intermediate size. The eosinophilia was notable, infiltrating the bronchial muscle to some extent, but most striking in the bronchial lymph nodes. The medium sized, and a few of the larger, bronchi showed sacculations, some of which were quite deep, each extending through an hiatus in the musculature, but with the thickened basement membrane always intact. Many of the sacculations had their origin at the mouths of the mucous glands, which were quite prominent. In some areas in the cartilage there was slight eosinophilic infiltration, but no destruction. In many small bronchi there were plugs of fibrin and desquamated epithelium, while many of the medium-sized bronchi contained Curschmann's spirals. An acute fibrinopurulent bronchitis was noted. The thymus was persistent and hyperplastic with fatty atrophy.

Case Summary. An asthma of sudden onset such as this, occurring in a 50-year-old man, and following influenza, may be accepted as "bacterial" in origin. After only eight months'

duration in which the disease fairly overwhelmed him, death occurred in an attack at the end of three days spent in the hospital, during which time he had been almost continuously in asthmatic orthopnea. The significant pathologic findings were: (1) Marked hyaline thickening of the basement membrane; (2) slight hypertrophy of the bronchial musculature; (3) marked eosinophilia, seen also in the bronchial lymph nodes; (4) extensive sacculations; (5) partial occlusion of many lumina by exudate; (6) prominent mucous glands.

Case IV. L. B. (Path. No. A-306-AG), a 58-year-old farmer, was under observation in the medical service of the University Hospital from May 21, 1929, until his death on June 12 of that year. His chief complaint was of vague gastric distress, and secondarily of asthmatic attacks, chiefly nocturnal, for two years. Physical signs in the chest were typical of bronchial asthma. The blood eosinophilia was 12 per cent. Sensitization tests were not done. Evidence of upper respiratory infection, or of accessory nasal sinusitis, was lacking. During his stay in the hospital the patient had almost nightly severe asthmatic paroxysms, which but infrequently responded to ephedrin and adrenalin. On the day of his death he developed a severe asthmatic attack, which resisted the most heroic measures of medication, and he died after practically two hours' continuous asthmatic dyspnea.

Autopsy was performed three hours after death. On each side, the diaphragm was at the level of the sixth rib. The lungs were voluminous. The thymus was well represented by fatty remains. The heart measured 13 by 10 by 4 cm. and weighed 280 gms., with a left ventricular wall thickness of 1.7 cm. The right heart, moderately dilated, showed subepicardial fatty infiltration. The lungs had a combined weight of 600 gms. and presented a striking emphysema. The thickened bronchi stood out from the cut surface, with obvious narrowing of their lumina. Apart from congestion, no other changes were noted except for a moderate, generalized atherosclerosis. A culture from the heart's blood showed no growth.

Microscopic Examination. The atrophic myocardium showed degenerative fatty infiltration, and there was marked subepicardial fatty change. The most marked features in the lungs were the extreme emphysema and the narrowing of the medium-sized bronchi. This latter was accomplished by infolding of the mucosa in irregular fashion, creating longitudinal rugae of varying heights. The mucosa, always intact, was thick, and beneath it there was a markedly thickened, hyalinized basement membrane present in bronchi of all orders. The intermediate bronchi showed further a thick, cellular subepithelial layer with but a slight eosinophilic infiltration. The musculature was markedly hypertrophic, but in an irregular fashion, interrupted at many points. The mucous glands were not prominent. At no point was there any marked eosinophilia. A few of the large bronchi contained granular mucinous material in small amounts with desquamated epithelium. Chronic purulent bronchitis and chronic passive congestion were the only other findings of note in the lungs.

Case Summary. No evidence can be adduced in this case as to the etiology of the condition. Sensitization tests were not carried out, but none of the findings, clinical or pathological, indicate a focus of bacterial infection. In spite of the age of the patient, and the short duration, this case can best be attributed to an allergic factor. The following are significant pathological findings: (1) Partial stenosis of medium-sized bronchi; (2) moderately thickened, hyalinized basement membrane; (3) marked hypertrophy of the bronchial musculature; (4) slight cellular exudate in the bronchi; (5) slight eosinophilia; (6) a thick, cellular subepithelial layer.

Case V. M. C. (Path. No. A-123-AG), was a 36-year-old construction foreman who gave a definite history of asthmatic attacks occurring almost daily from 1914 up to the time of admission to the University Hospital in April, 1928. At this admission studies pointed to a "bacterial" bronchial asthma, and he was discharged with autogenous vaccines made from the strains of *B. coli* and *Staphylococcus albus* to which he had shown positive sensitization tests. Readmitted in November, he reported that during the vaccine injections, the asthmatic attacks had become more frequent and more severe. The physical signs of bronchial asthma were present during both admissions. Blood eosinophilia was nine per cent. There was no definite evidence of sinus infection. Asthmatic paroxysms were frequent and severe during the second admission, with orthopnea even between the attacks. There were two to four attacks daily, responding generally to the administration of adrenalin. On the day of death the patient passed from one paroxysm to another for six hours.

Autopsy. The thorax was emphysematous in type. The heart measured 13 by 11 by 6 cm., weighed 345 gms., and showed a terminal right-sided cardiac dilatation of marked degree. The lungs showed a widespread and advanced emphysema with an area of atelectasis in the left lower lobe. The thickened bronchi stood out prominently and contained mucoid exudate. At the right base there was seen one small area of bronchopneumonia, not purulent. Mediastinal and bronchial nodes were hyperplastic.

Microscopic Examination. The heart showed only extensive fatty changes. The lungs, apart from the bronchi, showed chronic passive congestion, emphysema, patches of dense fibrosis, an old area of organizing fibroid pneumonia, and one area of recent purulent lobular pneumonia. The

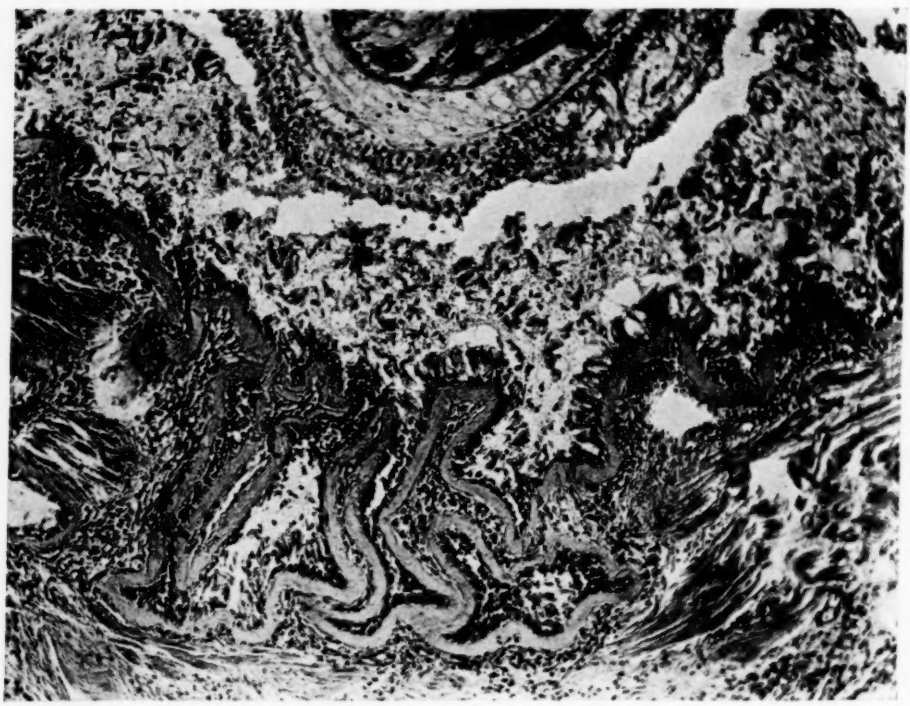

FIG. 2. Case V. Medium sized bronchus with marked hyaline thickening and folding of the basement membrane. Spiral plug of tough mucus in lumen. Marked chronic catarrh.

bronchial pathology was shown particularly by the bronchi of intermediate size, although the terminal bronchioles, in spite of dilatation, presented a marked hyaline change in the basement membrane, and the larger bronchi were thickened without the same accentuation of the basement membrane. The bronchi of medium size showed varying changes. In many the mucosa was thrown into folds of such height as to cause marked narrowing, but always with continuity of the well-marked, thickened and hyaline basement membrane except where pierced by the mouths of the mucous glands; others showed sacculations of considerable depth, and in these the mucous glands were distinctly hypertrophic. In some areas the bronchial lumina were filled with mucoid, homogeneous masses not of the Curschmann type, and poor in cells. The muscular hypertrophy was variable—quite marked in some bronchi, and almost negligible in others. A few small ulcerations of the bronchial mucosa were noted. The bronchial eosinophilia was quite striking, but there was no eosinophilia in the bronchial nodes. The main bronchi were notable in that they showed a marked hyaline change in a thickened basement membrane which extended also about the mucous glands. The thymus was hyperplastic. The liver showed healed miliary tubercles, and the gastrointestinal tract a chronic catarrh. An early arteriosclerotic atrophy of the kidney was present.

Case Summary. This case of 14 years' standing and said to be bacterial in origin was aggravated by the attempts to establish immunity to the supposedly offending organisms. Death occurred as a direct result of repeated seizures. The findings of interest are: (1) Thickening and hyaline change of the basement membrane; (2) the varying changes in the intermediate bronchi; (3) exudate in the bronchial lumina, mucoid and homogeneous; (4) small ulcerations of the bronchial mucosa; (5) marked bronchial eosinophilia.

Case VI. (Path. No. A-91-AI.) The first admission of R. B., a 13 year old girl, was to the Pediatric Service of the University Hospital in February, 1930. Her chief complaint was 'asthma'. A paternal grandmother had suffered from hay fever. Whoopingcough and chickenpox were the only events in the patient's medical history. Since early childhood there had occurred frequent asthmatic attacks with cough and sputum. She was quite ill on admission, with marked dyspnea, musical râles throughout the chest, and no consolidation. During her stay in the hospital, she developed a lobar pneumonia with subsequent empyema, which was drained by rib resection in April. Having been discharged towards the end of May, the patient was readmitted in September for recurrence of the asthmatic attacks. During this admission the thoracic sinus became healed. She was observed in many typical asthmatic attacks. Sensitization tests were positive for a large number of animal substances, food proteins and bacteria. The attacks of asthma became more frequent and more distressing during October with an alarming increase in her previously marked asthenia. On October 18 intratracheal lipiodol injection was done, radiographic study showing slight enlargement of the right lower bronchi, but no definite bronchiectasis. Following the lipiodol injection the patient complained of extreme nausea and vomited several times. She became cyanosed with gradual diminution of pulse pressure, and respiration ceased on the following day about 20 hours after lipiodol injection.

Autopsy. The thorax was symmetrical, showing on the right side posteriorly, a 5 by 2½ cm., well-healed scar over the site of the eleventh rib. The inner meninges were extremely congested and edematous. The right pleural space was entirely obliterated by adhesions which posteriorly assumed the aspect of heavy scar tissue about the thoracostomy wound. Dense pleural adhesions were present on the right side. The thymus was large. Notable in the heart was moderate right ventricular hypertrophy, the wall measuring 7 mm. in thickness and consisting entirely of muscle. The left lung measured 22 by 15 by 5 cm. and weighed 370 gms.

Congestion and edema of the lung parenchyma were noted. The small bronchi showed moderate dilatation, the larger bronchi hypertrophy, and the lumina of the latter a tenacious, mucoid exudate. The right lung was slightly smaller in volume, 18 by 12 by 8 cm., but weighed 740 gms. and showed marked edema. In the main bronchus was found a tough fibrinous membrane forming a complete cast extending into the bronchi of the second order. In the intermediate bronchi were found many plugs of mucoid exudate, while the smaller bronchi were dilated. In the larynx and trachea the mucosa was covered with a mucopurulent exudate.

Microscopic Examination. Atrophy of the heart was apparent, with Zenker's necrosis, fatty degenerative infiltration of the myocardium and relative increase in stroma. The aorta was hypoplastic; the pulmonary artery, slightly atheromatous. In general, the lungs showed chronic passive congestion with an acute exacerbation and edema. Curschmann's spirals were present in many of the bronchi. The bronchi of intermediate size showed the most marked thickening of the bronchial wall, especially muscular hypertrophy with eosinophilic infiltration. Hyaline thickening of the basement membrane in the bronchi of all sizes, even those of less than 1 mm. outside diameter, was marked. The large bronchi were without the same degree of thickening presented by those of medium size. Superimposed on these changes was an acute purulent bronchitis and a hyperplasia of the mucous glands. Both in the bronchial lumina and throughout the lung were numerous oil droplets which had not given rise to any reaction. The bronchial nodes were infiltrated with eosinophiles. Except for hypoplasia of the adrenals equivalent to that of the aorta, there were no other notable findings.

Case Summary. This child had suffered from asthmatic attacks for many years, and it should be noted that sensitization tests, carefully carried out, indicated that she was hypersensitive to several types of allergens. In conformity with this, it is a reasonable conjecture that her death was due to an allergic reaction to lipiodol. Of note in the pathologic findings are: (1) A marked hyaline thickening of the basement membrane comparable to that found in the preceding cases; (2) distinct muscular hypertrophy in the bronchi of medium size; (3) distinct eosinophilic infiltration of the bronchial walls and of the lymphnodes; (4) hyperplasia of the mucous glands.

Case VII. S. K. (Path. No. A-343-AH), a white male of 56 years of age was first admitted to the University Hospital on April 25, 1930. His chief complaint was 'asthma', which was of three years' standing, and the onset of which he attributed to the forced inhalation of fumes from the spraying of lacquer paint in the factory where he was working. With the asthma there occurred swelling of the face and feet, palpitation, and two months later, hay fever, which was shown by sensitization tests to be due to ragweed. Two sinus operations were followed by pneumonia which confined him to bed for 14 weeks. A course of 'injections' was given with no benefit. The hay fever recurred each summer; the asthma, palpitation and edema became worse as time went on, and there were frequent attacks of abdominal colic. In the family history, the mother had had asthma, while other immediate relatives had suffered from rheumatic conditions, tuberculosis, and cancer. When admitted the patient was extremely weak, in an asthmatic (cardiac?) condition, but during his stay in the hospital he suffered many typical asthmatic paroxysms. The blood eosinophilia was six per cent. Acute abdominal pain was a frequent complaint, for which no cause was determined. A rapidly developing pneumonia in the right lower lobe caused death on May 8, 1930.

Autopsy. The body was dolichomorphic in type, with evidence of recent loss of weight and the appearance of premature senility. The lungs were voluminous, filling the anterior mediastinum, and the cardiac apex was at the level of the fifth rib, inside the midclavicular line. The heart, except for

some atherosclerosis of the aortic cusps, and terminal right-sided cardiac failure, was not remarkable. The lungs together weighed 1260 gms., the right lower lobe showing practically complete consolidation. The left lung, extremely voluminous, presented marked thickening of the bronchial walls, which projected above the cut surface of the organ. Splenic, hepatic, mesenteric and peritoneal tubercles of varying ages were found.

Microscopic Examination. The heart, in addition to subepicardial fatty change, showed marked endocardial sclerosis and fibrosis extending into the myocardium. The coronaries were markedly sclerotic, without obliteration. Extensive areas of croupous pneumonia in the right lower lobe showed partial organization of the fibrinous plugs in many alveoli. The emphysema was patchy and there was an acute exacerbation of a chronic passive congestion. All of the bronchi showed the changes characteristic of bronchial asthma. The medium-sized bronchi in particular had a hyaline basement membrane of unusual thickness. Most of the bronchi were filled with a tough mucin. There was an irregular folding of the mucosa of each of the bronchi as well as many sacculations which not infrequently passed entirely through the musculature at the mouths of the mucous glands. The bronchial musculature was very hypertrophic, and in a remarkably uniform fashion. The eosinophilic infiltration was less marked than that seen in the other cases with the same degree of alteration of the mucosa, and there were no eosinophiles in the bronchial nodes. Acute purulent bronchitis and areas of bronchopneumonia completed the pulmonary pathology. In the bronchial nodes were encapsulated, caseating tubercles. Generalized atherosclerosis, ar-

FIG. 3. Medium sized bronchus with hyaline thickening of basement membrane and localized area of metaplasia of epithelium to squamous type. Chronic catarrhal bronchitis. Changes characteristic of bronchial asthma.

teriosclerotic nephropathy, and fibroid atrophy of the testes were noteworthy findings.

Case Summary. This case resembles number II of the series in that the onset of the asthma was attributed to the inhalation of chemical fumes, with the subsequent establishment of a diagnosis of hay fever on a protein-allergic basis occurring at intervals, concomitantly with the asthma. As a further contribution towards possible etiology is the record of two (evidently) radical sinus operations. Further should be noted the 19 weeks' illness with 'pneumonia' and the absence of benefit from 'injections'. Pathological features of interest are: (1) An unusually thick, hyaline basement membrane; (2) the presence of mucosal foldings, as well as many sacculations; (3) marked uniform hypertrophy of the bronchial musculature; (4) slight degree of eosinophilia; (5) mucinous exudate in the bronchi; (6) hyperplasia of the mucous glands.

Case VIII. S. A. (Path. No. A-142-AG), a 58-year-old white female admitted to the Gynecology service of the University Hospital in 1927 for vaginal bleeding, had suffered from asthma since the age of 13. She had had pneumonia at least four times. The asthmatic attacks had increased in frequency in the preceding few years. In 1928, following irradiation for a pelvic neoplasm at intervals during the year, she returned to the hospital critically ill and died in a few hours.

Autopsy. There was a remarkable facial hypertrichosis, although the body hair was normal in distribution and amount. Lung borders were 2 cm. apart in the anterior mediastinum. Areas of lymphoid tissue were apparent in the thymic fat. The heart presented a distinct relative right-sided preponderance (right ventricular wall, 11 mm. thick; left, 17 mm.), and a terminal right-sided failure. The lungs showed purulent bronchopneumonia. There was an apparent increase of fibrous tissue along the bronchial tree and many of the bronchi were dilated. There were adenomas in the thyroid gland. In the body of the uterus there was a sloughing, neoplastic mass with much scar tissue adjacent to it.

Microscopic Examination. Diffuse fatty change and endocardial sclerosis were seen in the heart with slight localized fibrosis of the myocardium. The lungs showed an acute purulent bronchitis with acute purulent bronchopneumonia. In areas there was a marked hypertrophy of the bronchial epithelium, amounting in places to a metaplasia to a stratified type. Quite as prominent as this was the almost universally thickened and markedly hyalinized basement membrane. The bronchial lumina varied widely in configuration—some quite regular, others presenting extensive sacculations, often through the musculature, but always with continuity of the basement membrane. The subepithelial layer was moderately thickened. All the bronchial lumina were widened. The muscular layer was distinctly hypertrophic. In none of the bronchi, or any of the lymph nodes, was there any degree of eosinophilia. The greater part of the body of the uterus was replaced by a peritheliomatous angiosarcoma, probably arising in a leiomyoma.

Case Summary. The interest in this case lies in the duration of the disease —45 years. The age of onset and the absence of foci of infection would indicate that this case did not belong to the class of bacterial asthmas. In view of the long standing pulmonary disease, the following are of interest: (1) Marked hypertrophy of the bronchial epithelium; (2) universally thickened and markedly hyalinized basement membrane; (3) distinct hypertrophy of the bronchial musculature, though not greater in degree than in some of the preceding cases; (4) extensive sacculations of the bronchi; (5) moderate thickening of the subepithelial layer;

(6) widening of all the bronchial lumina; (7) absence of eosinophilia.

Discussion

From a clinical viewpoint, in each of these eight cases the criteria of bronchial asthma were established. Five of them died from the immediate results of asthmatic paroxysms. In the last three cases the cause of death was intercurrent infection or neoplasm, thus making possible a contrasting study with those in which the asthmatic phenomena were predominant at death. The duration of the disease in this series of cases varied from eight months to 45 years, the age of the patient from 13 to 75 years. According to the classification still employed clinically, cases I, III, and V would be termed 'bacterial', while cases II, IV, and VIII probably conform to the negative appellation of one writer—"non-bacterial allergic asthma". In the remaining two cases sensitization tests and clinical evidence make it clear that the individual was not only hypersensitive to certain allergens but also had foci of infection usually accepted as being of paramount importance in 'bacterial' asthma.

The clinical evidence of bronchial asthma and its periodic dramatic crises with which the older writers were mainly concerned are too well known to bear repetition. It should be re-

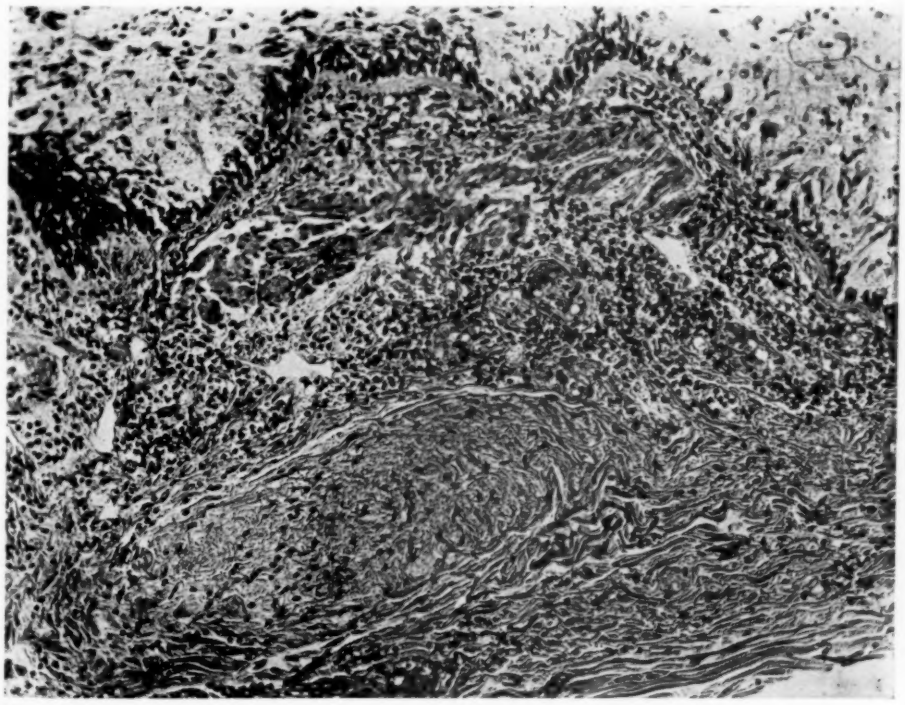

Fig. 4. Medium sized bronchus from case of bronchial asthma, showing hypertrophy of the smooth muscle in the wall. Hyaline thickening of basement membrane and cellular infiltration. Many of the cells in this infiltration are eosinophiles.

marked, however, in support of the statement of Huber and Koessler,[7] that the coincidence of blood and sputum eosinophilia is pathognomonic of the disease, pulmonary distomiasis and hydatid disease alone excepted.

Constitutional Pathology

In reviewing the gross and microscopic findings in these cases, one is impressed by certain constantly recurring evidences of constitutional pathology. These center about the lymphoid apparatus and the chromaffinic and vascular tissues. Table I (p. *272*) shows the remarkable manner in which all these cases conform in essential detail to the state known as the thymicolymphatic constitution. Many of these cases, in spite of the fact that all had reached middle age except one child of 13, showed well-defined thymic remains even grossly, while all but one showed microscopic evidence of general lymphoid hyperplasia. Every case presents hypoplasia of the adrenals and of the aorta. As to physical habitus some of these patients were of the asthenic dolichomorphic type of the thymicolymphatic constitution while others were of the gouty-arthritic habitus.

Local Pathology

Dealing with the local pathological changes, the microscopic features of the bronchial and peribronchial tissues are of the greatest interest. Most constant are those occurring in the basement membrane. In this series, variable as it is in respect to apparent etiology, age of the patients, and duration of the disease, the basement membrane changes are striking in their uniformity. These are two in number, thickening and hyalinization, as first noted by Mönckeberg.[8] Which is primary cannot be said with certainty, for both are well marked in the case of only eight months' standing. Always marked in the intermediate bronchi, these changes may extend into the smallest bronchioles, and in certain instances are most extreme in the large bronchi. The absolute and unvarying continuity of the membrane changes no matter how extensive the sacculations, or how high the mucosal rugae, is a matter of note. For many years this basement membrane change has been recognized in this laboratory as an invariable finding in asthmatic conditions. How advanced this change may become is illustrated by case V, of 14 years' standing, in which the thickened and hyaline basement membrane in the main bronchi extends even about the mucous glands (figure 2). This case is also of interest in showing small ulcerations of the bronchial mucosa—a finding previously noted by Kountz and Alexander[3] and Berkart.[9] In the other case of long duration (number VIII, 45 years), the epithelium presents a marked hypertrophy. Increased cellularity has led to some increased thickness of the subepithelial layer in practically all the cases, but is most evident in case IV. In this layer the eosinophilia, when present at all, is generally most prominent.

Second only to the basement membrane change in constancy, is the hypertrophy of the bronchial musculature. That the degree of hypertrophy is not proportionate to the duration of the disease is shown by the fact that case IV two years after onset has the most marked muscular hypertrophy which

far outshadows that seen in case VIII after 45 years of asthma. In accord with this is the finding of only an irregularly distributed muscular hypertrophy in case V of 14 years' duration, while case III after eight months presents a uniform hypertrophy of slight degree. It is therefore quite evident that some other factor or factors must enter into the mechanism of the asthmatic orthopnea.

Einthoven[10] first proved (1892) by experiments later duplicated by Brodie and Dixon[11] (1903), that stimulation of the peripheral end of the vagus in itself was sufficient to produce stenosis of the bronchi, due to a contraction of the muscle fibers. Dixon further found that the same phenomenon occurred in a decerebrate animal by irritation of the nasal mucous membrane. In 1909 Mönckeberg[8] first noted histologically an hypertrophy of the bronchial musculature in an asthmatic, and this, together with Auer's statement[12] that the anaphylactic process takes place in animals in which the vagus nerves had been cut long enough to produce degeneration of the nerve endings, not only enabled Meltzer[13] to explain asthma on the basis of allergy, but apparently vanquished those proponents of the "mucosal edema" theory of bronchospasm, who stressed the activity of the bronchial exudative system. (*Vide* Faschingbauer,[14] Unverricht.[15]) In the experimental animal, peripheral vagal stimulation doubtless produces preeminently a spasmodic contracture of the bronchial musculature, but the analogy to the asthmatic state is only apparent, and modified by many other factors, intrinsic and extraneous. Experimental proof is not lacking that vagal stimulation produces in addition vasodilatation, and that the nerve carries secretory fibers to the bronchial glandular system. In the asthmatic individual on an allergic or other basis, with the chronicity of the condition, and probably some degree of chronic infection superimposed, it is apparent that the neurogenic substrate is much altered as compared to the experimental animal. With this much evident, reference to cases III, IV, V, and VIII makes it apparent that the histopathology taken in correlation with the clinical course of these cases substantiates the suggestion of Alexander[16] that the bronchoconstriction is in reality due to a combination of all the effects of peripheral vagal stimulation, namely muscular contraction, vasodilatation, and glandular secretion, with one or the other assuming the dominant rôle in the individual case. The argument as to the respective importance of the muscular contraction and the "mucosal edema" is therefore quite pointless.

In conformation with this is the varying degree of hyperplasia and prominence of the mucous glands. In case IV, which presented the most marked muscular hypertrophy, the glands were atrophic.

The frequency of tissue eosinophilia in asthma has long been recognized, and the nature of the eosinotactic stimulus a point of controversy. In five cases of this series the eosinophilia was a notable feature; its absence in two of the remaining three is possibly to be accounted for by the presence of superimposed predominant pulmonary infection which overshadows the asthmatic process. The degree of eosinophilic infiltration was highly variable. Several

cases showed infiltration of the bronchial musculature and, to a slight degree, even of the cartilage, but in none was there the erosion and destruction of cartilage noted by certain observers.[3] The subepithelial layer contained the largest number of eosinophiles, but they may be spread outside the cartilage and be prominent in the peribronchial tissues. In cases III and VI the bronchial lymph nodes were remarkably infiltrated. Clinically, the blood eosinophilia is a most constant feature in this series, ranging from six per cent to thirteen per cent. One author,[5] in attempting to differentiate the histopathology in "bacterial" and "non-bacterial allergic" asthma, has made the claim that eosinophilia is practically absent in the former, and constant in the allergic type. All three of the present cases that could be considered "bacterial" showed a marked eosinophilia, even infiltrating the muscle and bronchial nodes in case III, while case IV, which was without suggestion of bacterial etiology, showed only a slight eosinophilia although dying in an asthmatic crisis.

Although founded on the postulates laid down by such observers as Virchow, Marchand, and Ribbert (perivascular lymphoma), the conception of true autochthonous tissue eosinophilia cannot be accepted. The massing of the eosinophile cells varies in location from subepithelial to peribronchial layers, may be absent at some points, occurs in the bronchial nodes, and in the spleen and thymus (Huber and Koessler), and in some cases the eosinophiles can be seen in great numbers about the bronchial capillaries. Schlecht first proved (1910) that blood eosinophilia occurred regularly as part of the anaphylactic process upon reinjecting sensitized animals. Recently Unverricht[15] drew attention to the fact that Schilling has proved definitely the production of eosinophiles in the bone marrow, their entrance into the blood stream, and their mobilization in the lungs from the blood in the anaphylactic animal. Moreover, the eosinophiles were found to disappear wholly from the circulating blood at the onset of the anaphylactic seizure, subsequently reappearing and becoming more numerous. Upon extirpation of the spleen or its exposure to x-ray, the eosinophiles in the circulating blood were increased; whereas, conversely, the injection of splenic juice caused a reduction of the blood eosinophilia. The eosinophilic increase, then, in the circulating blood and tissue is most reasonably regarded as a generalized hematopoietic response, designed for protection against the foreign allergic substance, be it bacterial, peptone, amine or chemical, but acting as an eosinophilotactic stimulus. Its absence is generally due to some superimposed infection which assumes dominance, and in response to which the leukopoietic function is altered. This has recently been proved by the work of McGregor on experimental sinus infection in animals, in which the introduction of a fresh infection caused the complete disappearance of eosinophiles from the tissues in a relatively short time.

In the guinea pig dead from an anaphylactic shock, the classical picture in the lung fields is the almost absolute stenosis of the bronchi due to obliteration of the lumen by infolding of the epithelium and contraction of the muscular layer. This has never

been exactly duplicated in man, although in one case reported by Boughton,[17] dying after the injection of 1 minim of horse serum, the microscopic picture in the lungs was very similar to that seen in the sensitized guinea pig. The opposite, however, is seen in most of the reported cases, as in this series, in which the most frequent finding is extensive sacculation interrupting the continuity of the muscular layer and extending through the mouths of the mucous glands, the latter evidently offering the necessary hiatus for the extension of the sacculations. Illustrating again the inconstancy of the bronchial changes is case V in which the bronchi in some instances present a mucosal infolding and partial stenosis suggestive of the anaphylactic guinea pig, while others are widely dilated with extensive sacculations—both of these occurring in a supposedly 'bacterial' type of asthma. Only in case IV (allergic?) is narrowing and stenosis of the bronchi at all generalized, although in two of the other cases, V ('bacterial'), and VII (doubtful etiology), the bronchi are much narrowed in some areas. In these three cases the bronchial stenosis has evidently been accomplished by infoldings and muscular spasm with exudate in the lumina playing a lesser part. In other cases the occlusion of the lumina is accomplished by the exudative products of the hyperplastic, bronchial mucous glands and mucosa (Curschmann's spirals, cellular débris). In practically all instances the smaller bronchioles are uniformly dilated, obviously the result of increased intrabronchial tension, which is in all probability also the cause of the bronchial sacculations. Of all the foregoing changes it should be remarked that their variation in distribution is such that many fields have to be examined before one can come to definite conclusions regarding the type of pathologic change predominant.

The study of the cardiac changes becomes of interest in the light of the claim made by Alexander *et al.*,[18] that the heart remains remarkably free from damage in long continued bronchial asthma. They established the criteria of bronchial asthma in 50 patients with a ten year average duration of the disease and found only four with any clinical evidence of cardiac impairment that could be attributed to the asthmatic condition. They suggested that the increased intrathoracic pressure impedes the return of venous blood to the heart, thus leaving less work for the heart to accomplish during an attack. This is not borne out by the almost constant ventricular hypertrophy in this series at autopsy. Including a 13-year-old girl, and without note of sex or build, the average thickness of the left ventricular wall in all eight cases was 18.25 mm., and of the right ventricular wall 7.87 mm. The case of longest duration (VIII) presented a distinct right-sided preponderance with a right ventricular wall of 11 mm. thickness. In spite of the fact that in each case the right ventricular wall is at least slightly increased in thickness, in only one (IV) is there any definite increase in subepicardial fat, while in two (III and VI) it is entirely muscular. Valvular lesions were lacking. The chief changes are atrophy, myocardial fatty infiltration, and patchy myocardial fibrosis.

Recent writings have referred to the

absence of associated tuberculosis,[15, 20] often mentioned by the older writers. Only three of our cases showed tuberculous lesions and these consisted of old healed tubercles in the bronchial nodes, and in the liver in one instance.

Etiology

Until the conception of allergy became applicable to asthma, all investigators directed their attention to the determination of the inciting factors producing the periodic, dramatic crises with which they were called upon to cope. It was Ehrlich's pupil, Otto, who published in 1906 the first systematic investigations and conclusions regarding anaphylaxis. Four years later Meltzer[13] suggested that asthma was an anaphylactic phenomenon, and that all asthmatics were sensitized to a specific substance. Forthwith a multitude of inciting factors were taken as proven, and the vial and needle of the immunologist became the chief weapons of the clinician against asthma. With von Pirquet's conception of human allergy, as contrasted to experimental anaphylaxis, certain factors were found necessary to establish the proof of a substance acting as an allergen, viz: (1) An exact anamnesis; (2) a positive cutaneous reaction; (3) the passive transference of the cutaneous reaction to a healthy person by the serum of the allergic patient (Prausnitz-Küstner reaction); (4) the proof of the existence of the allergen in the individual's environment; (5) reproduction at will of the allergic phenomena by exposure of the unprotected patient to the allergen, by inhalation, ingestion or injection; (6) disappearance of the symptoms by removal of the offending allergen. It soon became evident that only a small percentage of the cases studied were truly allergic, and for the susceptibility of the allergic individual, Coca[28] invoked the existence of an unknown immune body—the atopic reagen.

A variety of conditions thus became known as allergic manifestations—serum disease, hay fever, urticaria, certain types of enteritis and eczema, migraine, as well as bronchial asthma. In spite of the cases of asthma in which all the above postulates have been fulfilled, and many with apparent cure by reinjection of the specific allergen in desensitizing doses, there remain many cases in which none of the multitude of known allergens can be shown to be causative. And there are other findings which would indicate that there are more important, basic and underlying factors of which allergy is but an expression. Although only ten per cent of individuals are allergic in the ordinary sense of the term, Bloch and Karrer[20] demonstrated that practically any subject could be forced to allergic reaction; many bronchial asthmatics exist constantly in an environment laden with the specific allergen to which they are sensitive, and yet react only at irregular periods; many others, contrariwise, after removal to surroundings supposedly free from the causative factor do not necessarily improve and may even become worse; and finally, the proof is now overwhelming that the allergic substance, whatever it may be, is not necessarily protein in nature. Proof of this is found in the production by a non-protein extract of ragweed, of allergic phenomena exactly duplicating those ordinarily seen in cases sensitive to this plant.

An illustration of the latter, also, is the large group of cases showing susceptibility to chemical agents. Chief among this group are the coal tar derivatives—salicylic acid and its various derivatives and modification, antipyrin, methyl salicylate, benzoic acid and sodium acetate. Case I of this series, in spite of a 'bacterial' type of asthma, showed a definite susceptibility to, and severe paroxysms following, the administration of acetylsalicylic acid, death occurring in a seizure so induced. Van Leeuwen[19] reports a similar case of susceptibility to acetylsalicylic acid manifested by severe asthma suddenly developing in a woman who had taken the drug for years previously, and also cites the case of another asthmatic who was susceptible to antipyrin. He concludes that such hypersensitiveness is acquired through absorption from the gastrointestinal tract, with altered reaction to the molecule as it is in the blood stream. In the case of sudden death reported by Wright,[6] the asthmatic seizure commenced a short time after the administration of acetylsalicylic acid and codeine. Like van Leeuwen's case, adrenalin was ineffective. By no stretch of imagination can such results be interpreted as due to the actual toxicity of aspirin. This has been determined by de Jankovich,[21] who reported six cases of fatal poisoning with the only notable autopsy finding that of multiple hemorrhages, and fixed the lethal dose at 20 gms.

It is therefore evident that even as the atopic reagen in the hypersensitive individual is unknown, so is the specificity of the allergic antigen a matter of doubt. The basic laws of immunology demand that to establish the identity of a specific allergic reaction, the experimental repetition of passive sensitization with an antibody-containing serum must be proven. The inability to obtain such a reaction with many supposed allergic antigens makes it impossible to apply the general principles of so-called protein anaphylaxis to other forms of hypersensitiveness.

For this reason it seems impossible to accept as proven the conception of bacterial protein acting as a basic, allergic, etiologic factor to produce a clinical entity known as 'bacterial asthma'. Introduced by Walker[22] in 1917, the term was immediately adopted by clinicians as a most opportune label for those asthmatics who did not react to any known allergen, and in whom one could demonstrate the presence of focal infection, preferably in the accessory nasal sinuses, or existing as a chronic form of bronchitis. As early as 1922, Cooke,[23] in a critical review of Walker's work showed that the latter had demonstrated clinical improvement under nonspecific bacterial vaccine treatment, regardless of the reaction obtained with the bacterial protein used. Walker's results showed no conformity with local cutaneous reactions or recovery of specific organisms in the vaccines. Many of his best results were obtained with *Staphylococcus aureus* vaccine, although that organism had not been recovered. Cooke, in 50 cases of bronchial asthma, found only two which reacted to any type of organism with an immediate urticarial wheal, and even in these the bacteria to which they thus appeared sensitive could not be recovered from the sputum or nasal cultures. He was quite unable to elicit any constitutional re-

actions by the use of bacterial preparations as allergens, and concluded that they do not act as fundamental allergens *per se*, that the cutaneous test with bacterial preparations was useless, and that the conception of bacterial asthma was based entirely on analogy. Six year later, Zinsser[24] supported these conclusions and confessed to knowing of only one case where eradication of a sinus infection associated with bronchial asthma gave relief. Unger,[25] reporting 189 patients with bronchial asthma and hay fever treated by sensitization tests and injections in the clinic at Northwestern Medical School, is silent regarding any results with bacterial reactions or vaccines. It is a fact worthy of note that the cases in this series who received treatment with supposed specific vaccines uniformly became much worse; one case, during such treatment passing into a prolonged series of seizures that eventually resulted in death (case V).

The case against the specificity of bacterial allergens becomes even more convincing through the lack of any uniform pathological changes in the asthmatic so classed in spite of effort to establish such an entity. In a recent publication, Steinberg and Figley,[5] on the basis of autopsy findings in two cases attempted to differentiate the pathologic changes in 'non-bacterial allergic' and 'bacterial' asthma, referring particularly to the contrasts in emphysema, atelectasis, bronchial exudate, muscular hypertrophy, destruction of epithelium, and eosinophilia in the two types. Tables I and II show how variable the changes are in both types. This has been discussed already in regard to the eosinophilia; the epithelial destruction is more likely an evidence of activity of the process, while the other changes seem to vary in individual response, irrespective of etiology.

It is evident at least that in spite of the apparently well defined relation of the disease to allergy in a few cases, in the majority of instances we are without definite knowledge as to the underlying factors of asthmatic etiology. As

TABLE I
Evidences of the Thymicolymphatic Constitution

	THYMUS	LYMPHOID SYSTEM	ADRENALS	AORTA
CASE I	Persistent and hyperplastic	Hyperplastic	Hypoplastic	Hypoplastic
CASE II	Slightly persistent and hyperplastic	Sinus catarrh	Moderately hypoplastic in both cortex and medulla	Moderately hypoplastic
CASE III	Persistent	Hyperplastic	Hypoplastic	Hypoplastic
CASE IV	Persistent	Slightly hyperplastic	Markedly hypoplastic	Hypoplastic
CASE V	Persistent	Markedly hyperplastic	Hypoplastic	Markedly hypoplastic
CASE VI	Persistent and hyperplastic	Hyperplastic	Hypoplastic	Hypoplastic
CASE VII	Very marked and persistent hyperplasia	Markedly hyperplastic	Hypoplastic	Markedly hypoplastic
CASE VIII	Persistent and hyperplastic	Hyperplastic	Moderately hypoplastic	Moderately hypoplastic

TABLE II

Bronchial Pathology

CASE NO.	DURATION OF DISEASE	LUMINA	EPITHELIUM	BASEMENT MEMBRANE	SUBMUCOSAL LAYER	MUSCLE	MUCOUS GLANDS	BRONCHIAL NODES
I	5 years	Dilated. Some occluded. Curschmann's spirals.	Not remarkable	Thick and hyaline	Eosinophilia	Moderately hypertrophic	Prominent	
II	8 years	Dilated. Some occluded. Curschmann's spirals.	Not remarkable	Thick and hyaline	Eosinophilia	Hypertrophic	Prominent	
III	8 months	Dilated. Some occluded. Curschmann's spirals.	Not remarkable	Thick and hyaline	Eosinophilia	Slightly hypertrophic	Prominent	Marked eosinophilic infiltration
IV	2 years	Narrow. Slight cellular exudate.	Not remarkable	Thick and hyaline	Thickened. Cellular. Eosinophilia slight.	Markedly hypertrophic	Not Prominent	
V	14 years	Marked variation. Mucinous exudate.	Small ulcers	Very thick and hyaline	Eosinophilia	Irregularly hypertrophic	Hypertrophic	
VI	10 years (approx.)	Mucoid exudate	Not remarkable	Thick and hyaline	Eosinophilia	Hypertrophic	Hyperplastic	Eosinophilic infiltration
VII	3 years	Variable. Mucinous exudate	Not remarkable	Very thick and hyaline	No eosinophilia	Uniformly hypertrophic	Hyperplastic	
VIII	45 years	Universal dilatation. Extensive sacculations	Marked hypertrophy	Very thick and hyaline	Thickened. No eosinophilia.	Hypertrophic	Not Prominent	

to the actual inciting factor of the individual paroxysm, we are no nearer the truth than were the disciples of the school of Salerno, nor are we able to describe the dramatic phenomena in such graphic phrases as did Floyer in 1698. In general one can say that the symptoms are equivalent to an expression of hyperstimulation of the parasympathetic nervous system. Hansen,[26] in addressing the Royal Society of Medicine in 1929, correlated this fact with the conception of the psychophysic coordination of the individual by which the autonomic and vegetative nervous systems function in harmonious interrelation. Thus, by the reaction of the higher centers upon the more lowly neurogenic system, can one perceive some reason for the well established cases of asthma constantly exposed to the inciting allergen, but in whom the asthmatic paroxysm occurs generally after periods of mental stress.

Even with this rather vague hypothesis as a reason for onset in some cases, even with the possibility of van Leeuwen's late theory of 'colloid substances of unknown composition in the atmosphere', one is driven to seek a deeper anatomic substrate upon which these inciting factors act. In such a search, first of all, one is confronted by the frequent repetition of a familial history. The heredity of the allergic soil is a well known and established fact. In addition, the asthmatic, as Davidson[27] points out, often gives a family history not only of asthma, hay fever, urticaria and other definite allergic phenomena, but also nervous manifestations such as migraine, epilepsy, hysteria and other neuroses. The majority of cases of true asthma occur in middle aged people who show prematurely a degenerative reaction to the stress and strain of living, often with accompanying chronic bacterial infection, focal or otherwise. Such lowering of vital force is evidenced in several of the cases in this series by repeated and prolonged infections which in themselves would have been but transitory with the normal individual.

Seeking more definite anatomic and histologic evidence of deviation from the accepted normal, each case in this series shows conclusive evidence of a pathologic constitution. Table III shows the evidence of such in the lymphoid and chromaffinic tissues and in the vascular system. The thymicolymphatic constitution, persistent in later life, provides that receptive anatomic substrate in which the so-called allergic antigen is best able to elicit those diverse phenomena known as allergic reactions. It is reasonable to suppose that our designation 'allergen' may be applied in most instances to any substance which possesses the ability of acting upon this pathologic constitution in such a manner as to provoke an expression of its altered state. More specifically, the allergic state is an altered reaction, but it is the altered reaction of this inheritable, hypoplastic type of constitution often associated with an exudative diathesis, and upon which a multitude of exogenous, provocative factors, ordinarily without influence on a normal soil, are capable of producing the expressions of the diseased state. Such an individual may reach middle life before showing definite pathologic evidence of his constitution, and then, as in case III, under some added load as an acute infection,

TABLE III

Presumable Etiology and Cardiac Condition

CASE NO.	AGE	ETIOLOGY	TERMINAL CONDITION	LEFT VENTRICULAR WALL	RIGHT VENTRICULAR WALL	OTHER CARDIAC CHANGES.
I	43	Bacterial	Asthmatic paroxysms	20 mm.	8 mm.	Patchy myocardial fibrosis. Endocardial sclerosis.
II	75	Allergic	Asthmatic seizures, lobular pneumonia.	25 mm.	6 mm.	Myocardial atrophy, fibrosis. Endocardial sclerosis.
III	53	Bacterial	Asthmatic seizures	22 mm.	10 mm.	Fatty changes. Hypoplastic myocardium.
IV	58	Allergic (?)	Asthmatic paroxysms	17 mm.	6 mm.	Fatty changes. Atrophic myocardium.
V	36	Bacterial	Asthmatic paroxysms	20 mm.	6 mm.	Fatty changes.
VI	13	Both (?)	Lipiodol reaction	13 mm.	7 mm.	Myocardial atrophy and Zenker's necrosis.
VII	56	Both (?)	Lobar pneumonia	15 mm.	7 mm.	Endocardial sclerosis.
VIII	58	Allergic	Sarcoma of uterus: pneumonia.	17 mm.	11 mm.	Fatty change. Endocardial sclerosis.

inhalation of chemical fumes, or mental stress, may suddenly exhibit a profoundly altered reaction which may be so constantly severe and depressive as to bring about dissolution in a comparatively short time.

Summary

1. Eight cases of bronchial asthma with autopsy findings and microscopic studies are reported. In five of these death resulted during asthmatic paroxysms.

2. The chief local pathologic changes are—

a. Invariable thickening and hyaline change of the basement membrane of the bronchi.
b. Eosinophilia.
c. Varying degrees of muscular hypertrophy and glandular hyperplasia dependent upon the individual reaction to vagal (?) stimulation.
d. Bronchial sacculations occurring through the mouths of the mucous glands.
e. Epithelial changes such as hypertrophy and metaplasia, interpreted as evidence of chronicity.

3. Review of clinical, immunological and pathologic evidence fails to support the conception of such an entity as bacterial bronchial asthma.

4. Each of the cases of this series is proven to be of a thymicolymphatic constitution. It is suggested that bronchial asthma and many other 'allergic' phenomena are but the expression of the response of this inheritable constitution to exogenous substances—'allergens'.

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Chronic Appendicitis*

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More half hours may be spent puzzling over whether to operate for chronic appendicitis or not than over any other major surgical condition. By the time a patient with gallbladder disease consents to operation, the symptoms are usually definite, and in the great majority of cases there have been sharp colics. Those suffering from goiter usually wait until they are nervous and have lost weight before consulting a surgeon. Patients with cancer or with peptic ulcer usually have well defined clinical pictures by the time of operation. On the other hand, the public is so well informed and apprehensive of delay in appendicitis that patients usually seek operation immediately if appendicitis is diagnosed.

Discussion will be limited to chronic appendicitis—with pain, usually of long duration, either repeated or persistent, in the right lower quadrant, with no rise in temperature nor leukocytosis.

Diagnosis

There is a voluminous literature, which I will not attempt to review. Each year brings forth its quota of critical analyses of cases, positive opinions or impressions, diatribes against appendectomy unless that organ be acutely inflammed, etc.; and if one glances over several of these, or some of the reviews, he will be surprised at the wide differences of opinion still existing as to the indications for what is apparently one of the simplest operative procedures we do. On one side is Carnett[1] who states that "there is no such clinical entity as chronic appendicitis"; and that pain in the right side is very frequently due to intercostal neuralgia, which can even simulate acute appendicitis. On the other side are several noted internists as Rehfuss and Boas, surgeons as Deaver, who, while picking their cases carefully and refusing to operate upon or have operated upon the majority of those complaining of right sided pain, nevertheless state positively that appendectomy does cure chronic pain in the right side, even chronic pain in the upper abdomen with right lower quadrant tenderness; and that sometimes the diagnosis is most difficult, being made only after right lower quadrant exploration, and then is not definite until one has followed the patient and he remains free from pain. Gaither,[2] in a careful review based upon 1,000 cases, concludes that: "chronic appendicitis is at the present day a widespread and often unrecognized malady; it is often masked by the prominence of its secondary manifestations; it should be thought of in all cases of disordered digestion presenting motor and

*Received for publication, August 25, 1931.

secretory symptoms, in every case of chronic constipation, in gastric upsets without definite ulcer symptoms, in intestinal dyspepsia and toxemic states".

Figures can easily be obtained showing that to operate, or not to operate, for chronic appendicitis is indeed a major problem.

Lichty,[3] analyzing 517 consecutive cases in which "the complaints after the operation were the same as before the operation", found that in 243, or almost one-half of them, appendectomy had been performed for chronic appendicitis. Andresen[4] found that ten per cent of the total admissions to his gastro-intestinal clinic at the Long Island College Hospital had had an appendectomy, and that among similar cases in private practice there were 13 per cent who had had appendectomy. Others have put this figure as high as 25 per cent.

There is no doubt but that many appendectomies are part of a long chain of useless and now discarded operations. These started with ovariotomy; then included operations for retrodisplaced uterus; chronic salpingitis; adhesions; various uplifts for neuralgia, as movable kidney, ptotic stomach and bowel; chronic cholecystitis, finally reaching the appendix. Indeed, these procedures have in the past all been done for this same chronic abdominal pain, generally right sided. But there is also no doubt that most of these procedures, judiciously employed for chronic complaints, produce striking and grateful cures.

During the past five to ten years, several surgical clinics have carefully analyzed their results following appendectomy, with the realization that though there are still considerable differences of opinion, certain types are more clearly seen as potential poor results, and operation avoided. Poor results with persistence of symptoms, range from 10 to 70 per cent, frequently quoted as 30 to 40 per cent. There are several analyses, in which three to four years after 30 to 40 per cent of failures were reported following appendectomy, 10 per cent of failures are now reported.

There is rather general agreement that two types of chronic appendicitis can be differentiated.

1. Repeated painful attacks, usually starting with an acute attack. There are only one or two dissenters from the opinion that such patients should have appendectomy, and that this generally brings relief. Several state that if appendectomy were limited to cases in which repeated attacks with intervening free intervals were described, the operation, patient and surgeon would be much better off. "It is a wise rule never to diagnose chronic appendicitis and never to operate upon such a case without a history, definite or perhaps even indefinite, localized or with referred symptoms, which may be regarded as a probable attack of acute or subacute appendicitis", says Thomas R. Brown.[5] This viewpoint is rapidly gaining adherents.

Rolleston, Aschoff, Alvarez, and Seale Harris, have all stated that all chronic appendicitis cases have had previous attacks. Lichty[3] makes no diagnosis of appendicitis unless there have been characteristic acute attacks.

2. There is a second group, described alike by no two writers, in which most of the difficulty and confusion lie. This is made up of cases

of persistent right-sided pain with reflex gastro-intestinal symptoms of various forms.

Crohn[6] has described these cases under four groupings:

I. Young adult men, in whom the distress simulates gastric or duodenal ulcer, probably due to pylorospasm. There is not the periodicity usually associated with ulcer; in these cases the distress is more irregular and intermittent; it comes long after meals, two to three hours; is usually located just above the umbilicus, and there are long free intervals.

II. Patients who have had obstinate constipation for years, with mild reflex gastric symptoms:— heartburn, pyrosis soon after eating, halitosis, bad taste in the mouth, poor appetite. Sometimes there is no abdominal pain. Occasionally a case of this type will develop a sudden severe gangrenous appendicitis.

III. Indefinite and continuous low abdominal pain in the right lower quadrant, sometimes in the right hypochondrium. These cases simulate gallbladder disease, or occasionally new growth. When heartburn, belching and poor appetite occur in the neurotic, there is a natural tendency to make light of these symptoms.

IV. Unusual cases presenting chiefly diarrhea with no gastric symptoms. There may be severe upper abdominal cramps with nausea and vomiting, and no right lower quadrant tenderness.

There is a good deal of difference as to operative indication in this group. Deaver insists that pylorospasm with distressing dyspepsia may be of appendiceal origin even if there is no right lower quadrant tenderness, and will be cured by appendectomy. Boas and Rehfuss, also, sometimes advise appendectomy for chronic abdominal complaints as a diagnostic procedure. If the symptoms are relieved, the diagnosis is correct. Most other recent writers dissent from this viewpoint, and urge extreme caution in cases with no recurrent attacks.

Failures

Perhaps most can be learned from analyses of failures. Several of these, from very careful follow-up services, have been reported recently.

Whipple[7] analyzed 53 failures making the following final diagnoses in these cases:

Neuroses of various types	21
Visceroptosis	8
Colonic stasis—spastic descending colon	3
Tender cecum bound to adnexa	2
Tuberculous lymphadenitis	1 or 2 each
Cholecystitis	
Gastric ulcer	
Duodenal ulcer	
Sacro-iliac sprain	
Chronic colitis	
Pulmonary tuberculosis	

He cautioned against operating upon (a) those asthenic ptotic individuals belonging to the so-called carnivorous type with a long standing history of pain and tenderness in the right lower quadrant, and (b) those having many and exaggerated complaints, among them pain and tenderness in the right lower quadrant. These patients have neuroses of one kind or another and may be either the well nourished or the ptotic type.

A similar list of 230 diagnoses in private patients who had had appendectomy without relief is given by Andresen:[4]

Gastroduodenal ulcer	36 per cent
Gastritis and duodenitis	26 per cent
Gallbladder disease	35 per cent
Colitis	21 per cent
Pancreatitis	0.4 per cent
Adhesions	25 per cent
Hernia	7 per cent
Hemorrhoids	7.5 per cent
Carcinoma	3 per cent
Food allergy	7 per cent

Gibson's[8] conclusions are frequently quoted and bear repetition. To avoid disappointment he advises:

1. Comprehensive and detailed history taking.
2. Careful physical examination.
3. Excessive care before advising operation in women and all more mature individuals.
4. Careful search at time of operation for other lesions.
5. The sedulous avoidance of operations upon neurasthenics.
6. Restraint, if there are no definite attacks or localized pain with nausea or vomiting.
7. A good sized incision and a thorough exploration.

Another study of end results, where 26 per cent of unsatisfactory results are recorded, ends as follows:[9]

"The following points should be seriously considered in making a definite diagnosis of chronic appendicitis with a promise of permanent relief by operation:

1. A complete detailed history of frank attacks. The nearer the history approaches the cardinal signs of appendicitis the better the prognosis for cure.
2. Physical examination should be most thorough, ruling out especially genito-urinary and gynecological conditions and not overlooking lung pathology.
3. Asthenic individuals, both male and female, with a suggestive neurotic make up should be subjected to long periods of observation with all refinements of diagnosis.
4. Large incision.
5. The finding of a diseased appendix is not enough to guarantee the patient complete relief.
6. Delivering the appendix through a small incision and the use of dry sponges may favor the formation of adhesions."

Note the similarity in the conclusions arrived at in these two studies.

Some of the facts brought out by these postoperative analyses of failures—and they all agree in substance—are: Beware if there are no acute attacks. There are more failures in women than in men. There are more appendectomies performed for chronic appendicitis in women than in men, and the ratio should be more nearly the ratio of appendectomy for acute appendicitis in women and men respectively. Everyone who has analyzed his results urges one to beware of the neurasthenic, the neurotic, the long, thin visceroptotic persons of both sexes. They had best be left alone, or operated upon after very careful observation and exclusion of all other possible causes of abdominal pain and discomfort. One hospital reduced its failures from ten per cent to one per cent by first referring suspected chronic appendicitis cases to a psychiatrist.

Discussion

From the above analyses, plus my own experience, the following generalizations can be made:

Needless to say, chronic appendicitis should always be an exclusion diagnosis. Certain types and age groups are more apt to have chronic appendicitis. All analyses have shown that complicating conditions—ulcer, gallbladder disease, ureteral and kidney conditions, etc.—are more frequent the older the patient. In children, the attacks may be milder, and are more frequently overlooked. The tenderness and pain may be located higher, at the level of the umbilicus, because the cecum frequently lies higher. There is not the confusion of diagnosis which ulcer, gallbladder disease, salpingitis, etc., bring in later life, but there is more apt to be abdominal pain referred from pulmonary or upper respiratory infection than in adults. In-

cidentally, the incidence of acute appendicitis is higher in epidemics of upper respiratory infections than at other times. Personally, I am more apt to believe a child when he complains of transient, but repeated bellyache than an adult, and think these cases usually are appendicitis. If in doubt I tell the mother that the child probably has appendicitis, should be watched carefully, and taken care of at the first recurrence of trouble. I have removed some surprisingly involved appendices in children after mild attacks, and do not recall as many postoperative failures as in adults. A normal child should not know he has a "stomach", and repeated unexplained "bellyaches" can be considered more significant in children than in adults.

Ureteral Calculus

Ureteral calculus is not hard to avoid if one is on guard. None of the postoperative analyses record more than two or three cases which subsequently proved to be urinary calculi. A calculus in a young adult usually gives a severely painful seizure, with the pain out of all proportion to the local findings. The cases I have had the most difficulty with have been between 35 and 50 years of age, generally heavy set men, with a dull right-sided ache. A few white blood cells may be all the urinary findings given by a large kidney stone. When there is the slightest doubt, I look at the sediment myself.

Gallbladder Disease

The gallbladder is coming to the fore as the chief rival of the appendix. Disease of this organ is now one of the most frequent affections for which laparotomy is undertaken. It is being diagnosed earlier in life than formerly, and since the Graham-Cole test (which has a high degree of accuracy), is being found more frequently.

Graham believed that the majority of cases in which symptoms were thought to be due to chronic appendicitis are due to gallbladder disease and spastic constipation. Indeed, Jordan and Lahey[10] recommended that if certain abdominal symptoms — gas, distress, and more or less atypical pain— do not respond to rest in bed, bland diet, etc., cholecystectomy is sometimes indicated, even if the gall bladder fills well with the dye. I have had one such case in a heavy set man, whom appendectomy failed to relieve of mild but persistent dyspepsia. The gallbladder filled well, was grossly normal on removal, but microscopically showed chronic inflammation of moderate degree. The patient has remained free of abdominal distress he had had for years. Irland[11] goes one step further and feels that the gallbladder may be frequently responsible for symptoms which in no way implicate the digestive tract, the gallbladder acting as a silent focus of infection.

This important rôle of the gallbladder has been stressed only for the past few years. Perhaps some of the poor results in patients classed as neurasthenics have this explanation.

Spastic Constipation and Allergy

Students of diseases of the colon feel that this organ is more frequently deranged than is the stomach "although the stomach has had more advertising". Its most common malfunction is a condition of localized spasm, caused by undue muscular tonus which, in turn,

probably results from abnormal nervous stimuli—imbalance of the sympathetic nervous plexuses governing the colon. Duke, Vaughan, Rowe[12] and others feel that these manifestations are allergic in nature and due to food sensitization. Cramps and flatulence are produced, and similar heightened neurogenic secretory stimuli produce mucous diarrhea. These localized spasms can occur throughout its extent, but are more common in the descending colon. When prolonged, intestinal stasis is produced proximalward, which may easily result in secondary dilatation and tenderness in the cecum, the rolling, gas-filled cecum which was thought significant of chronic appendicitis. Kantor[13] feels that the position of the cecum is important clinically. If it is high-lying, there are few symptoms. If low-lying, symptoms are common, the drag of the colon on adjacent organs (possibly the duodenum) perhaps being responsible.

Eggleston[14] reported that 22 per cent of 100 spastic colon cases had had appendectomy without relief. These individuals, preponderantly women, long, thin, visceroptotic, with cold extremities, low blood pressure, easily fatigued, "belly conscious", are avoided by all who know. Their dyspepsia, flatulence, cramps, and diarrhea are expressions of motor and secretory dysfunction of the colon due either to sympathetic nervous system imbalance, or perhaps localized allergic spasm and edema, and are not to be explained upon an anatomical basis such as appendectomy might cure.

Another pitfall which has been recognized recently is abdominal allergy —abdominal pains due to food sensitiveness. Osler [15] wrote an article in 1904, "On the surgical importance of visceral crises in the erythema group of skin diseases", cautioning against the danger of unnecessary surgery. Since then, the old fashioned angioneurotic edema, or urticaria, modernly conceived as the characteristic lesion of allergy, is made to explain a host of apparently unrelated phenomena. Muscular spasm and mucosal congestion and edema, the pathological changes in allergy, can occur anywhere in the body. In the brain, they are said to produce cerebral edema for which decompressions or fifth nerve injections have been done. In the alimentary canal, canker sores, coated tongue, ulcer-like pains, gastro-intestinal bleeding, pruritus ani have all been ascribed to local sensitization of various parts of the alimentary mucous membrane.[12] The liver cells and gallbladder mucosa becoming edematous, cause right hypochondriac pain for which gallbladders have been removed. Urinary symptoms (dysuria, frequency, etc.), some forms of hypertension, hypotension, disturbed menstruation, are all described as due to sensitization to certain foods or other articles. A localized spasm of the Fallopian tube has been reported as simulating ectopic pregnancy; the sting of *Pediculus pubis*, or of the bed bug is presumably due to a localized allergy from the toxins excreted.

Seriously, however, food allergy may cause various atypical abdominal symptoms; pains, colics, distress, distention, nausea, pyrosis, vomiting, spastic constipation, diarrhea and colitis. The pains are more often generalized and in the lower abdomen. Appendectomy has been performed frequently when the pains could have

been cured by elimination of certain foods, generally wheat, milk or eggs. More important still, distress continues until the offending factor is sought out and eliminated.

The following case history demonstrates the confusing picture which abdominal allergic manifestations may present.

S. M. was a boy, aged 13 years. On his first visit to the clinic in June, 1929, it was noted that he had had two attacks of pain in the right lower quadrant, each of two weeks' duration. During the attacks, pain came two or three times daily, with no relation to food. Flexing the right thigh and lying down stopped the pain. There was slight tenderness over McBurney's point, and the x-ray diagnosis was disease of the appendix.

He returned on April 12, 1930, having recently had another attack, this time with the pain confined chiefly to the epigastrium. Because of marked dermographia he was referred to the allergy clinic (Dr. Geo. L. Waldbott) for study. It was found that he had had eczema; his father and one sister also had had eczema. There was no other positive finding except an eosinophilia of seven per cent. He was sensitive to cheese, wheat, beef, asparagus, rabbit hair, eggs, and chicken feathers. Under treatment by means of elimination of these articles aided by injection of their extracts the child did very well until the ragweed season started, when there was vomiting, abdominal pains, upper respiratory catarrh and exacerbation of the eczema. On one occasion, injections of ragweed produced severe pain in the abdomen. There has been occasional slight recurrence of pains and sensitiveness, but the boy had gained 15 pounds and was much improved when last seen in March, 1931.

One must be careful here. I have seen attacks recur after the patient was supposedly cured by treatment directed against food allergy, necessitating appendectomy.

Other Conditions

It is well to remember also that sacro-iliac disease causes anterior abdominal tenderness. (Baer's point). A three-eighths inch lift on the right heel has corrected a lumbar lordosis for which three operations on the abdomen had been done. Tuberculosis and cancer of the cecum are frequently indistinguishable from chronic appendicitis.

As noted, many writers state that unless there is tenderness in the right lower quadrant no operation should be undertaken. I have had three patients in whom there was no right lower quadrant tenderness and in whom definite chronic appendicitis was found.

The rare or unusual case of appendicitis can simulate almost any intra-abdominal disease—depending chiefly upon its position. Ewald[15] in 1899 introduced the term "appendicitis larvata" to describe cases where "the pain of which the patient complains, leads him and the doctor in the first instance to anything but an illness originating in connection with the appendix". Pain under the left costal margin; at the right costal margin (appendix lying underneath the liver), or behind the kidney, may be the only symptom of appendicitis. An appendix plastered in the pelvis, or wrapped about the sigmoid or rectum may give diarrhea, vomiting, loss of weight, mass, etc., exactly simulating carcinoma.[16] Underneath all the coils of intestine, it may simulate mild subacute obstruction. Hematemesis and hematuria can be caused by chronic appendicitis.

X-Ray Diagnosis

A battle royal has raged concerning the value of X-ray examination in chronic appendicitis. Filling, non-filling, segmentation, delayed emptying, tenderness over the appendix, etc., all have proponents and opponents. An

important practical consideration frequently concerns whether a patient of moderate means should be subjected to the (for him, considerable) expense of an X-ray examination. The late Dr. Carman of the Mayo Clinic was rather disdainful of the diagnostic value of the X-ray in appendicitis, and this was well known.

Deaver expressed himself rather forcefully:[17]

"It is my experience that if a careful study of the history with painstaking physical examination does not make the diagnosis it will usually not be made by the roentgen ray study.

"Cholecystography and roentgen ray examination have not given me so much satisfaction in differentiating between the chronic gallbladder and the chronic appendix as have a carefully taken history and a carefully conducted physical examination."

One internist states that the main cause of needless appendectomies is the "furor operandi" of ambitious surgeons, whose chief aid and abettor is the roentgenologist. Rehfuss blamed the disinterested surgeon and said he never saw a surgeon fluoroscope a patient, and a surgeon was no more competent to pass upon X-ray evidence than a roentgenologist was to remove the appendix.

As with everything, there is a middle course. Lahey's opinion was: "Expertly applied, wisely interpreted and properly correlated no one can question its (roentgenological examination of the appendix) inestimable value."[18]

Merritt and Moore[19] very recently have stated that: " . . . by many, this subject (X-ray examination of the appendix) has been unheeded, and the method has failed, we believe, to receive the consideration that it merits."

The X-ray examination is sometimes more informative than other examinations, as in the following case:

Mrs. N. P., aged 42 years, was first seen August 11, 1930, complaining of "indigestion" and gas on the stomach. For several months she had had occasional spells of indigestion. During the past two months, she had had three attacks of more generalized abdominal pain, lasting two to three days, accompanied by watery diarrhea. The pain was more on the left than the right side of the abdomen. There was no constipation. She had been on ulcer regime for five weeks. She had been in the country during the summer and there was some question about the well water used, several people having had diarrhea.

Examination revealed a pale, frail, ptotic woman, negative except for some general soreness over the left side of the abdomen, none elsewhere. X-ray (Drs. Evans and Reynolds) showed a long pelvic appendix which was tender, and retained barium 72 hours even though the cecum was empty.

Because the clinical picture was not clear, she was observed further. After one or two more general abdominal pain attacks, she developed a typical attack with pain in the upper abdomen shortly followed by soreness and acute tenderness in the right lower quadrant.

Operation revealed a long appendix, the midportion dilated by two moderate sized concretions, the tip thickened and sclerotic. She has remained well since the operation.

A roentgen examination which shows a tender, fixed appendix, is very helpful diagnostically. Tenderness moving with shifting of the appendix, is also diagnostic. A persistent kink representing adhesions at that site, or adhesions about the terminal ileum means disease in a high proportion of cases. If abdominal palpation elsewhere causes pain over the appendix, or pressure over the visualized appendix causes pain in other parts of the abdomen, this is significant.

On the other hand, "beading", seg-

mentation of the lumen, and incompetency of the ileocecal valve, are found frequently in normal persons. Stasis and delayed emptying certainly are not of as much importance as originally considered. Moore and Merritt[19] do not mention any of these as X-ray signs of appendicitis. Kantor,[13] from extensive X-ray and clinical studies of these cases, found that cecal stasis was even more common after appendectomy for chronic appendicitis than before operation, (27 per cent unoperated, 29 per cent appendectomized individuals) and adds facetiously that if the appendix were not removed, "there would be more stasis in it after operation than before".*

Unquestionably the chief usefulness of the gastro-intestinal series in these cases lies in excluding ulcer, gallbladder disease, and diseases of the colon, not forgetting the diagnostic aid of the flat kidney plate, and the help that establishing the anatomical position of the appendix gives in certain cases. Ulcer and appendicitis sometimes exist together. Deaver speaks of this. I do not think the incidence is as high as some have stated; maybe five to ten per cent would be correct. As mentioned above, several who have written on the subject feel that there is no upper abdominal dyspepsia which is cured by appendectomy. However, if the X-ray shows an irritable stomach, without ulcer, and a tender appendix, that, I think, is confirmatory evidence of appendicitis. But, after this is said my experience corresponds to the trend of recent opinion; there is a gradual rebirth or renaissance of the idea that a half hour's questioning, perhaps repeated two to three times, plus careful abdominal palpation is more valuable to the patient than most of the expensive tests. The follow-up studies generally note this. In their conclusions as to how to avoid unsatisfactory results, there is little mention of X-ray examinations, but all stress careful pre-operative history and examination, and knowledge of which types to avoid.

*Personal communication.

Operation

A word about the operation. There is a general feeling that it is devoid of mortality and complications, but there is a recorded mortality of 1.5 to 2 per cent in very good hospitals. I have never used a McBurney incision. Gibson,[8] after his first analysis of failures in 1920, gave up the McBurney and uses entirely a large rectus incision, for exploration. However, a wide operative exploration is not a panacea for right-sided abdominal pain. In 73 of 102 cases it did not avert an unsatisfactory result.

Concerning the appearance of the appendix at operation, there is no doubt but that partial or irregular or complete obliteration of the lumen indicates a chronic process and relief will follow operation. Fecaliths are plugs of intestinal contents which have become stagnant in the appendix lumen and become inspissated, encrusted with mucous, lime salts, etc. Their presence is presumptive assurance of a good result. The doubtful types are where one finds only slight congestion, a dulling of the normal lustre of the serosal surface, or coiling or slight kinking of the appendix—appearances which one frequently sees when operating for disease of other intra-abdominal organs,

and which seem like rather meager pathological changes upon which to explain all the patient's symptoms and to be the *piece de resistance* of all the study, trouble, and expense the patient and doctor have gone through.

There is controversy here. Some deny that these slight findings represent chronic appendicitis. The truth is that the border line between pathological and physiological change in the appendix probably has not been defined; and that, as stated above, the only proof in many cases is that, having followed these patients and found them free from pain after operation, they probably had appendicitis. In other words, the preoperative examination may be more accurate than the findings at operation.

End Results

I have summarized 50 of my own personal records of patients upon whom appendectomies had been done for chronic appendicitis in whom I knew the end results, followed three to six months later. All acute appendicitis cases were excluded. All these cases had had long continued pains, had normal temperature and normal blood count. There were no fatalities, and no postoperative complications. Thirty-seven cases had had previous attacks of right lower quadrant pain, with approximate freedom from pain between attacks and no other symptoms. As near as I know all of these were relieved. I either have a note that the patient was well or free from symptoms three to six months later, or a note from the attending physician that such was the case.

Of the remaining 13, there were four cases where there had been epigastric distress associated with right lower quadrant attacks. One of these cases had an X-ray diagnosis of prepyloric and duodenal ulcer. All of these patients are cured following appendectomy.

Another case developed heartburn shortly after appendectomy (definite appendicitis was found at operation). Her pains in the right side have ceased, but she still has occasional heartburn relieved by alkalies. Two cases had only epigastric pain—no right lower quadrant symptoms, but examination revealed tenderness there. They were cured. Two cases had persistent right lower quadrant pain with no definite acute attacks. They are relieved. Three cases are unrelieved. One may have a chronic cholecystitis, the other two probably belong to the irritable colon group.

In one case, I made a frank error. This patient was vomiting, had abdominal pain, and also complained of deafness in the right ear, which I told her she could have attended to later. This deafness and the vomiting were due to central nervous system lues affecting the internal ear mechanism. It cleared up after antiluetic therapy.

Thus 75 per cent of the group had repeated attacks of right lower quadrant pain only, and all were cured. In the remaining group several were relieved of epigastric distress by appendectomy, and there is an occasional operation for persistent right sided pain or persistent epigastric distress, with good results. All of the four failures are found among these more atypical cases.

The age group as a whole is young: 2 over 40, 6 between 30 and 40, 17 between 20 and 30, 15 between 10 and

20. There are apparently no examples of chronic appendicitis in this series under 10 years of age. Although chronic appendicitis does occur in young children, most children under 10 years have acute appendicitis or a recurring acute attack. Incidentally, during the period of this series, there was one case in which operation was advised against, and the patient subsequently was completely relieved by appendectomy done elsewhere; also two cases in which operation was refused and the patients have remained well.

The series is not large, perhaps all subsequent histories and later developments are not completely known and perhaps some patients might have gotten well without operation. However, the review of these cases leaves the reiterated impression: It is time well spent when chronic appendicitis is suspected to examine a patient two or three times for one-half hour each time before deciding to do an operation. In this examination, the interpretation of the clinical history is the most important single factor in avoiding poor results.

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Clinical Teaching with Special Reference to Bedside Study of Disease*†

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THE word "clinical" means to lie in bed. Clinical medicine in its broadest sense means that part of medicine which has to do with the bedside investigation of disease in the living body. Clinical medicine is not a school of dogma; it is a school of method. Progress in clinical medicine is not hedged about by fixed limits, but may go as far as the individual's methods of observation and investigation can carry him.

The medical student should be impressed with this fact early in the course of his studies, because there can be no better preparation of the soil for the growth of observation, or for the budding and flowering of genius than the knowledge of an open course where all who enter the race are equally free and independent in the development of their talents.

In the middle of the sixteenth century Montanus first taught medicine by bedside instruction at Padua. He was contemporary with Vesalius, who was at this time preparing the Fabrica for publication, laying the foundation for modern anatomy, and giving it a place in the curriculum which it has never lost. We may safely say that clinical teaching dates from this period at Padua, but there was little progress during a period of three hundred years.

The awakening which came in the first part of the nineteenth century ultimately placed medicine on a broad basis. Lavoisier became one of the prime movers through his discovery of the nature of respiration and the sources of animal heat. The movement gathered impetus through the enthusiastic studies in gross pathology, carried on in France by Bichat and his followers, and in Vienna by Rokitansky and Skoda. Also through the development of percussion and auscultation by Corvisart, Laennec, Bayle, Piorry, Louis, and Andral.

While some mistakes were made and false conclusions drawn, the study of pathological anatomy and the more intelligent use of percussion and auscultation put clinical medicine forward with a bound. This was particularly true with reference to diseases of the heart and lungs. Wherever possible the symptomatic classification of disease gave place to the anatomic classification. Through these methods bedside study and observation received a great stimulus and there soon came a

*Received for publication, November 7, 1931.

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better understanding of many diseases. Laennec made his significant contributions to our knowledge of diseases of the heart and lungs; Louis through his clinical and anatomical study of disease, and his statistical and analytical methods not only made valuable additions to our knowledge, but he exerted a remarkable influence on the teaching of clinical medicine. It might be said that modern clinical teaching in America had its origin in the young American students of Louis during the fourth decade of the nineteenth century. Among these were Jackson, Shattuck, Holmes, Gerhard, Stille, Power, Flint, Swett, and Clark.

With the growth of clinical medicine have come all the influences of physiology, bacteriology, physiological chemistry and the various laboratory and mechanical aids to diagnosis, all designed to supplement clinical diagnosis, yet many of them serving as a dangerous lure for the unwary student of bedside medicine. He is often tempted to think of this or that test or device as a short-cut, rather than an aid to diagnosis or a method of confirming clinical findings, and may make the fatal mistake of slighting the history of the case and omitting or abbreviating the bedside study while he awaits the laboratory report. When the report is received, it may be given unwarranted weight, because there is nothing in the scale with which its value may be checked.

The bedside study of a case should begin with a carefully taken history and should not end until every organ in the body has been thoroughly examined. The true spirit of the faithful observer is expressed in the following quotation from Louis' Researches on Phthisis:

> "All these cases were taken on the same principles and with the same details; and as it appeared to me impossible to carry on a system of observation such as this and attend to private practice at one and the same time, I relinquished the latter altogether for the time being. I regularly passed three or four, and sometimes five hours daily in the hospital, devoting at least two hours to each postmortem examination. And although habit must have familiarized me with anatomical investigation, I still employ the same time I did two years ago in the examination. For I am convinced that if we wish to observe well, we must not observe hastily; and that the sole means of rectifying unfavorable errors is repeatedly to submit to new examination, questions which we may have at one time believed settled, and consequently to go on perpetually observing the same objects, just as if they were, in each instance, beheld for the first time."

William Harvey also possessed the spirit which should animate the true clinician when he said:

> "Let us then blush, in this so ample and so wonderful field of nature to credit other men's traditions only. *Nature* herself must be our adviser; the path she walks must be our walk; for so while we confer with our own eyes, and take our rise from meaner things to higher, we shall at length be received into her closest secrets."

The teacher of clinical medicine today carries a heavy responsibility. The "primal sympathy of man for man" which gave origin to medicine is being threatened by the various distracting diagnostic and therapeutic agencies, which, through spectacular appeal, or the promise of a short-cut, tend to draw the student away from the bedside.

While our knowledge of disease and its treatment has been greatly aug-

mented in the past century, and while this increased knowledge has materially altered our diagnostic methods and our therapeutic procedures, it has in no way altered the relation of host and disease. Human nature is just the same: disease untreated, works the same ravages in the human organism. The need of sympathetic understanding is still eminent. The clinical teacher must cultivate the *art* of medicine; his manner must be such as to inspire confidence and hope, and yet "the seeing eye, the hearing ear, the sensitive fingers and the understanding mind" must be employed with such searching effect that they approach the accuracy of a science. With these qualifications the teacher of clinical medicine should stand in relation to the student as a guide at the threshold of this most intricate and interesting unit of society, the human organism, ready to acquaint him with the normal living anatomy and physiology; prepared to elicit the history of disease; ready to demonstrate the methods of physical exploration for the purpose of discovering departures from the normal; quick to sense mental and psychological deviations; trained in the correlation and diagnostic appraisement of facts obtained; generous but discriminating in the use of laboratory and mechanical aids, and finally conservative and humane in the application of treatment. I think this is not too much to ask of the clinical teacher; the more he brings to the bedside, the more he will take away.

The student can be interested in the methodical demonstration of the normal and the discovery of departures from the normal. It is a mistake to allow him to go through medical school with the impression that if he learns anatomy, physiology, biological chemistry and bacteriology he will then be suddenly endowed with so-called diagnostic instinct, or as Oliver Wendell Holmes says "intuitive sagacity". He must learn that intuitive sagacity is synonymous with hard discipline and that every individual is endowed with special senses which if properly trained, may become powerful instruments of precision, incredibly keen and penetrating in their search of knowledge, and to go on the trail of disease with such weapons is like playing an interesting game.

Doctor Henry A. Christian has said:

"Perhaps the fault of the student is, more than we admit, a reflected fault of the teacher. We are constantly criticized through our students' work by their plunging immediately into instrumental and laboratory methods of examination of patients. Is not that the thing that we are doing ourselves a great deal more than we should, if we remember that we stand before our students as exemplars? Are we not too much inclined to fail to commit ourselves definitely to a certain finding as normal or abnormal after simple methods of examination? I am very sure that I am guilty often in that respect, notwithstanding that I rather carry it on my conscience to be guiltless as far as possible. As teachers we refer too readily to the x-ray or examinations of that special sort. I do not mean at all to decry reference to the x-ray, but we refer the patient for special examinations before we commit ourselves in the presence of the students to our judgment about the matter based on history and simple methods of examination. It seems to me we need to go over our patients with our students, using simple methods of examination, as soon as they come into the clinic or into the hospital; put down what we find; draw a conclusion; and then let other methods check up. It is not necessary, then, to argue with the student either the

merits or the limitations of the simple method. You are shown to be correct or incorrect, and in time the student will learn both your ability to use simple methods of examination and your failures in so far as your limitations are set by these other methods."

With these facts in view it would seem wise for medical school curricula to offer more bedside instruction and less amphitheater surgery. May the spirit of such men as Sydenham, Boerhaave, Laennec, Allbutt, and Osler inhabit the wards of every teaching hospital in order that the simple methods of bedside investigation may be preserved and that the knowledge of clinical medicine may reach its ultimate refinement!

Wastage of Health and Money in Sectarian Cults

"THE objection to the existence of sectarians is not so much that their therapeutic methods are in themselves incorrect as that the use of these or any other therapeutic measures by individuals untrained in the medical sciences, unable to diagnose disease, and unaware of their own limitations, is unsound, dangerous, and economically wasteful. It is established beyond doubt that in some disease conditions cures may be effected through the prompt employment of the appropriate remedial measures—early surgical intervention for cancer and acute appendicitis, antitoxin for diphtheria, quinine for malaria, salvarsan for syphilis, etc. Delay in the diagnosis of these conditions and in the employment of the proper remedy may result in a more serious illness than might otherwise occur, or may even result in death. There is danger not only to the individual but also to the community. How foolish it is for a community to maintain an elaborate public health machinery to prevent the spread of certain communicable diseases, and yet permit individuals to practice who are unable to differentiate diphtheria from pneumonia or scarlet fever from measles. In experimenting with sectarians, people often spend large amounts of money which they can ill afford."

From *The Healing Cults—A Study of Sectarian Medical Practice: Its Extent, and Control.* By LOUIS S. REED, PH.D. The Committee on the Costs of Medical Care, 910 Seventeenth Street, N.W., Washington, D.C.

Editorials

DEATH FOLLOWING THE USE OF ACETYLSALICYLIC ACID IN ASTHMATIC CONDITIONS

Notwithstanding the growing literature with constantly multiplying reports which detail serious untoward effects and even death following the use of acetylsalicylic acid in attempting to obtain relief from asthmatic conditions, further emphasis of this danger is indicated. An illustrative case is to be found in this issue of the ANNALS. In Case I of the group of patients described by Dr. Macdonald[1] it had been noted on several occasions that severe attacks of asthma had followed the administration of coal-tar products. Finally, one-half hour after taking 10 grains (0.6 gm.) of aspirin, the patient suffered a severe attack of asthma in the course of which death occurred. In discussing the etiology of this condition, Macdonald gives a brief review of earlier reports of similar fatalities, and calls attention to the fact that it is altogether out of the question to attribute the fatal outcome under such circumstances to the toxicity of acetylsalicylic acid in the ordinary sense of the term. He quotes de Jankovich on this point to the effect that the lethal dose can be fixed at 20 gms. The ill-effects which have been observed following the ingestion of but 5 or 10 grains (0.3 to 0.6 gm.) must have an allergic basis.

A recent coroner's case in the experience of the writer apparently falls in this group. A robust-appearing young man consulted a druggist for symptoms which he believed indicated a "cold". He was given two remedies of which one was acetylsalicylic acid in 5 gr. tablets. He took two of these tablets before leaving the store. Whether he took others is not known. Several hours later he was found in bed extremely dyspneic and cyanotic, and died before a physician could be obtained. Attention is called also to the recent paper by Lamson and Thomas[2] describing four examples of allergic response, one fatal, following the use of a nostrum for the treatment of asthma, the chief ingredients of which are acetylsalicylic acid and caffeine. The frequency of such ill-effects might lead to the impression that in some way a synergistic effect exists between the asthmatic state and acetylsalicylic acid. Rather must we recognize the pathologic constitution (thymico-lymphatic) which is the common substrate for the allergic response in both instances.

It is indeed with truth that Walzer[3]

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wrote: "Aspirin and the closely related coal-tar products are among the most treacherous drugs employed in the therapy of asthma. Their routine or careless prescription for atopic patients is a dangerous practice."

CARDIAC HISTOPATHOLOGY IN THYROTOXICOSIS AND ADENOMATOUS GOITER

Whether there are characteristic histopathological changes, or any changes at all for that matter, in the hearts of patients who have shown clinical evidences of cardiac disturbances in association with thyrotoxicosis has been subject to much difference of opinion. The staff of the Department of Pathology has recently conducted a purely objective investigation of this problem, a preliminary report of the results of which is to appear in a forthcoming number of the *American Heart Journal*. In connection with other lines of investigation which are described in that report, from a total of 43 autopsies of cases of exophthalmic goiter, 35 were selected as being free from evidences of syphilis, rheumatic fever, infective endocarditis or severe coronary atherosclerosis so that as far as possible known causes of myocardial changes were eliminated. A control series was then set up by matching each individual case of the exophthalmic series with another of the same age and sex, i.e., with a case as similar as possible in all respects except that exophthalmic goiter had not been present. Comparable microscopical slides from the hearts of these 70 cases were then examined and the results tabulated as to thirteen items commonly made note of in such examinations of the heart wall. In comparing the two series by this method only four features were found to occur with sufficiently greater frequency in the exophthalmic series to suggest that they might be significant. These were myocardial hypoplasia, fibrosis of the myocardium, endocardial sclerosis and cellular infiltrations. Myocardial hypoplasia was judged largely by the state of the muscle of the right ventricle. Its significance is that of constitutional pathology, vascular hypoplasia being a constant finding in the Graves' constitution.

Of the hearts in the exophthalmic series, 80 per cent showed myocardial fibrosis as compared with 51.5 per cent in the control series. The areas of fibrosis were usually small and were found chiefly in the left ventricular wall and the papillary muscles. The type of the fibrosis was such that it could not have been due to arteriolar occlusion. In four instances cellular infiltrations associated with patchy fibrosis were found, but in none of these were early lesions of the muscle fibers themselves seen, and the wandering cells were relatively few. In one case only was there a severe active myocarditis of the type described by Fahr. In this heart there were many focal lesions occurring throughout the myocardium, even in the auricles. These lesions were non-purulent and were present in all stages of a series extending from focal necroses with lymphocyte and plasma cell infiltrations to old and somewhat hyaline patches of fibrosis. As far as histopathological study could determine, such changes as were present in this heart would be entirely capable of leading to the areas of fibrosis found in a large proportion of the

exophthalmic series. If such was their etiology, it is difficult to understand why, in such a relatively large series, only a single example should be found in a stage of noteworthy activity. Nevertheless, no other etiological factor than the hyperthyroid state could be found for that particular case.

The hearts of 55 cases of adenomatous and nodular colloid goiter were compared by the same method with a matched control series from non-goitrous individuals. No significant difference in the incidence of pathological changes could be discovered between the two series.

Abstracts

Über das Auftreten von Perikarditis nach Lungeninfarkten [The Occurrence of Pericarditis Following Pulmonary Infarction]. By PAUL WERMER. (Klin. Wochenschrift, 1932, xi, 329-330.)

The deplorable frequency of both spontaneous and post-operative venous thrombosis and pulmonary embolism in recent years has directed attention to the etiology and pathogenesis of pulmonary infarction, and justifies description of a clinical picture which the author believes has not previously been detailed—pericarditis resulting from infarction of the lung. The etiology of this condition is considered to be direct extension of the fibrinous pleuritis which is always found over the base of an infarct to the pleuropericardial layer (pericarditis externa) and then to the visceral pericardium. Characteristic cases are presented. In making the diagnosis the evidences of the initial pulmonary pathology will usually be clearcut. The sudden appearance of stabbing pain in the side, cough and dyspnea, after an operative procedure, together with evidences of collapse, pallor or cyanosis, tachycardia, and thin feeble pulse make the diagnosis of embolism of a small pulmonary artery extremely evident. To this picture the evidences of a pericarditis are added in the syndrome under consideration. Pericarditis having this etiology was characterized in the author's cases by the roughness of the friction sound, by its fugacity and by the severe pain in the cardiac region which was readily distinguishable from the pain produced directly by the infarct. Differential diagnosis between this and other forms of pericarditis is discussed. Since pulmonary infarction at times gives no clinical signs or symptoms, in the association of the two conditions here described may be found the cause of some examples of "idiopathic" pericarditis for which no explanation has hitherto been available.

The Amount of Epinephrin in Extracts of the Medulla, Cortex and Whole Suprarenal Gland of Rabbits, Pigs, Cattle, and Horses. By TAKEO KOZIMA, MAMORU NEMOTO, SHIZUKA SAITO, HIROSHI SATO, and TAISUKE SUZUKI. (The Tohoku Jr. of Exper. Med., Sendai, Japan, 1932, xix, 205-232.)

Extracts were made from the medulla, cortex and whole substance of suprarenal glands of oxen and horses, of the medulla and whole glands of pigs, and of the whole gland of rabbits. The epinephrin content of these extracts was estimated by means of the colorimetric method of Folin, Cannon and Denis; that of Suto; the rabbit intestine segment method; the blood pressure of the pithed dog; the cat paradoxical pupil reaction; the perfusion of toads' legs and rabbits' ears. The results obtained are presented in tabular form. The suprarenal gland of the horse gave similar values for epinephrin regardless of the methods applied, but the glands of rabbits, pigs and cattle gave variable results in respect to the methods used, and the character of these

variations differed with the various species as well. To explain these variations, which are confidently believed not to depend upon technical error, certain suggestions are made. It is possible that the active principles in the extracts should not be assumed to be adrenalin alone, but some mixture of adrenalin and allied substances. Or, extracts may contain besides adrenalin some substances which act to intensify the action of epinephrin in various degrees according to the test object employed. Perhaps both of these alternatives act together. As previously recorded, there was demonstrated in small amount in the adrenal cortex of cattle and horses that substance which gives a positive reaction to the Folin test but none to the Suto test or to the biological tests.

Observations on Heart Sounds with Particular Reference to Gallop Rhythm and Sounds of Auricular Origin. By A. Garrard Macleod, Frank N. Wilson and Paul S. Barker. (Proc. Soc. Exp. Biol. and Med., 1932, xxix, 1009-1010.)

Two Einthoven galvanometers coupled in tandem were used to record the electrocardiogram and the heart sounds simultaneously, and the electrical stethoscope manufactured by the Western Electric Company was used to convert the sounds into electrical variations. The study of a large number of phonocardiograms led to the following tentative conclusions: From the graphic standpoint gallop rhythm may be defined as a condition in which three sounds occur during each cardiac cycle. Several varieties may be distinguished. (a) Protodiastolic gallop rhythm in which the extra sound follows the second heart sound by a constant interval and occupies the same position in the cardiac cycle as the normal third heart sound. (b) Presystolic gallop rhythm in which the extra sound precedes the first heart sound by a constant interval, and is almost certainly of auricular origin. The onset of the extra sound falls within the P-R interval of the electrocardiogram. This appears to be the most common type of gallop rhythm. It is particularly frequent in cases of arterial hypertension. (c) Systolic gallop rhythm in which the extra sound falls within the limits of ventricular systole. This type of gallop rhythm is uncommon and apparently has no clinical significance. (d) Gallop rhythm due to audible auricular sounds when the P-R interval of the electrocardiogram is increased beyond normal limits in which case the extra sound may fall in any part of diastole. This should probably be considered a variety of presystolic gallop rhythm.

Production of Thyroid Hyperplasia in Rats and Mice by Administration of Methyl Cyanide. By A. W. Spence and David Marine. (Proc. Soc. Exp. Biol. and Med., 1932, xxix, 967-968.)

The senior author and his associates have shown previously that the daily subcutaneous administration of small doses of aliphatic cyanides to young rabbits of either sex, maintained on a diet of alfalfa hay and oats, will produce thyroid hyperplasia within 21 days. Methyl cyanide was found to be most potent in this respect. Rats were given daily subcutaneous injections of varying doses of methyl cyanide in water. After 21 days only very slight thyroid hyperemia was shown. After 28 days there was definite thyroid hypertrophy, but it was obvious that the thyroid of the rat was less reactive than that of the rabbit. With increased dosage for the intervening days the thyroids were larger and more hyperemic at the end of 36 days. Although there were individual variations, in general the thyroid reaction was proportional to the dosage. Only a slight thyroid reaction was produced in mice after periods of dosage of from 11 to 34 days.

Reviews

Surgery of the Chest. By GEORGE F. STRAUB, M.D., F.A.C.S. xx + 475 pages, 341 illustrations, including 68 in color. Charles C. Thomas, Springfield, Illinois. 1932. Price, $10.50 postpaid.

Although outside of the field of practice of most of the readers of the ANNALS, it is appropriate to give brief mention to this book. There is perhaps no other anatomical area for specialization in which community of knowledge is more essential on the part of the internist and surgeon than the thorax. Since this book presents the recent advances in this field and discusses the application of surgical methods to a considerable number of diseases usually first seen by the internist, this treatise must be of interest and value to that group. For the surgeon it describes technical procedures as well. Not only is this book well written but it gains much from its numerous illustrations, many of which are reproduced from drawings by the author. Skillful use has been made of an additional color in many of the figures. The format is excellent.

Lang's German-English Dictionary of Terms Used in Medicine and the Allied Sciences with their Pronunciation. Revised and edited by MILTON K. MEYERS, M.D., Neurologist to the Northern Liberties Hospital; Chief of Nerve Clinic, St. Agnes Hospital; Consulting Neurologist, Jewish Hospital, Philadelphia, etc. Fourth edition, enlarged. 926 pages. P. Blakiston's Son and Company, Philadelphia. Price, $10.00.

Practically every English-speaking reader of medical German, not born to the language, has made use of the earlier editions of Lang's German-English Dictionary of medical terms. Such a dictionary is, in fact, indispensable. The standard German-English dictionaries lack all except the more frequently used medical terms and cannot give the specific medical significance of many terms which have a common usage as well. This new edition has been entirely reset. This was made necessary by the addition of the pronunciation, in easily understood English syllables, of each word. Also 3,500 new words have been added, bringing the total to approximately 56,500 definitions. This gives a work which is not only satisfactory for the general reader of medical German but also an important aid to the translator or researcher. This new edition will be welcomed by the users of its predecessors. German remains the most important foreign language for the English-speaking physician.

Biochemistry in Internal Medicine. By MAX TRUMPER, Ph.D., Clinical Chemist and Toxicologist; formerly in charge of the Laboratories of Biochemistry of the Jefferson Medical College and Hospital, and of the Psycho-Biochemistry Laboratory, Graduate School of the University of Pennsylvania; and ABRAHAM CANTAROW, M.D., Instructor in Medicine, Jefferson Medical College; Assistant Attending Physician, Philadelphia General Hospital; in charge of Laboratory of Biochemistry, Jefferson Hospital; with a foreword by ELMER H. FUNK, M.D., Sutherland M. Prevost Professor of Therapeutics at Jefferson Medical College. 454 Pages, 11 figures. W. B. Saunders Company, Philadelphia. 1932. Price, in cloth, $5.50 net.

This book is designed to correlate the established facts of biochemistry with the ordinary diagnostic problems of internal medicine. It is not a laboratory manual and accordingly is not concerned with the details of laboratory procedures. Rather it aims to give the clinician a clear understanding of the significance of the results of laboratory investigations within the field of biochemistry and related sciences. Eight

chapters are devoted to consideration of the clinical aspects of fundamental metabolic processes in health and disease. Then follow ten chapters dealing with more highly specialized functions and the biochemical aspects of certain disease states. The final chapter is an outline of the chemical diagnostic features of various disorders, thus providing an indexed table of the clinical laboratory tests of a chemical nature which are informative in various disease conditions. The style is lucid, and highly technical discussions and matters which are yet largely controversial are omitted. Free use of section and paragraph headings in several styles of type emphasizes the logical arrangement. This is a well made book which promises to be very useful.

Physiotherapy: Its Principles and Practice. By F. Howard Humphris, M.D. (Brux.), F.R.C.P. (Edin.), M.R.C.S. (England), D.M.R. and E. (Camb.), Hon. Consulting X-ray Physician and Electrotherapist to Christ's Hospital; Hon. Consulting X-ray Physician and Electrotherapist to the London Clinic; Late Officer in Charge X-ray and Electrotherapeutic Departments, 3rd London General Hospital; Capt. R.A.M.C. (T.F.); Late Consulting X-ray Physician to the Force in Egypt; Major R.A.M.C.; Past President of the American Electrotherapeutic Association; Past Vice-President of the Section of Electrotherapeutics, Royal Society of Medcine: and Ralph E. Stuart-Webb, M.B., B.S. (Lond.), M.R.C.S., L.R.C.P.; with contributions by Frank Romer, M.R.C.S., L.R.C.P.; A. E. Hayward Pinch, F.R.C.S., M.R.C.P. and A. Gordon Watson, M.D. The Macmillan Company, New York, 1932. Price, $4.50.

Physiotherapy: Its Principles and Practice, as its full title indicates, is divided into two parts. In the introduction the author defines Physiotherapy as "the treatment of the patient by physical means, at the hands of the physician or by the art and skill of the surgeon" and he stresses the necessity of physiotherapists being medically trained. In the first part, "Principles", a very full and detailed description of the application and apparatus of the various physiotherapeutic agents is given, as well as a brief historical review of the older methods, such as static electricity and low and high voltage currents. Infra-red rays, being antagonistic to ultra-violet and X-rays, may be used to some extent as preventive and curative of X-ray lesions, it is stated.

"Radium Therapy", which is Dr. Pinch's contribution, is a chapter of but 17 pages. One may well question the wisdom of attempting to present such an important subject in so small a compass. Ample warning is given as to possible complications and sequelae.

"Massage and Manipulation" by Dr. Frank Romer is well done. He wisely urges medical men to be sure that they give their patients no reason for going to a "bone setter". A doctor should know how to prescribe massage, and what particular cases need it. X-ray plates should be made of joints, before manipulation, to make sure that no pathological lesion exists.

Because in this country spa treatment is less known and less popular than in England and on the Continent, the discussion of this method of physiotherapy is of interest. One wonders, however, about the wisdom of the inhalation of radio-active waters over several days, in view of recent knowledge of the effects of fixation in the skeleton. Dr. Watson aptly states that "all mineral waters cure some cases", although he feels that at present the claims of spas are too conservative. Quite naturally he stresses the advantages of the British spas. Melted paraffin-wax baths and foam therapy are less common physiotherapeutic agents.

Under "Practice" the use of physiotherapy and what may or may not be accomplished in various disturbances and diseases is considered. One feels that some statements of the results seem at times over-enthusiastic, but the gratifying effects in poliomyelitis we know are not exaggerated. Particularly interesting is the description of Krowler's method in the treatment of tuberculous laryngitis, "in which the patient himself directs a beam of sunlight down his own throat by means of an ordinary looking-glass and a laryngoscopic mirror, for about an hour a day". This has been used by some laryngologists in this country with

decidedly good results. Dermatological use of physiotherapeutic agents is so general as to require no comment. The last chapter on the treatment of "Various Diseases" is of some present day importance to the devotee of sports, as golfer's back, motorist's heel, rider's strain and tennis elbow are all optimistically treated.

Throughout, the author insists that the physiotherapist cooperate with the physician and surgeon. The book is of general interest and value to all practitioners, and of real practical assistance to one whose special field is physiotherapy. R.C.W.

Conquering Arthritis. By H. M. Margolis, M.D., x + 192 pp., 3 illustrations. The Macmillan Co., New York City, 1931. Price, $2.00.

"Conquering Arthritis" is the somewhat optimistic title of another of the growing stream of books written for certain classes of patients by specialists in the particular disease discussed. Readily comprehensible to the intelligent reader and written by experts without the bias of commercial interests, they do much to aid the physician in his professional duties and may prove to be invaluable to his patients. Faced with a problem made unusually difficult not only by its own complexities and uncertainties but also by the necessity of using non-technical phraseology, the author has produced a work which, with a minimum of dogma, succinctly and unemotionally states the present knowledge of the genesis and treatment of arthritis. After a brief review of the history of the disease, the discussion of chronic arthritis is introduced by a simple classification, the following forms being recognized: (1) Senescent arthritis, (2) static arthritis, (3) metabolic arthritis, and (4) infectious arthritis. Each of these forms is treated separately but the greater portion of the book is devoted to the fourth class, with a somewhat extended discussion of the relation of focal infection to inflammation of joints. Especial emphasis is placed upon the teeth and tonsils as foci of localization of streptococci. While the author treats this subject quite dispassionately, nevertheless the uncritical reader might well receive the impression that laboratory animals may show arthritic changes when injected with organisms from human focal infections irrespective of the mode of injection and further, that such changes, when they occur, constitute proof of the existence of arthrotropic organisms. The author considers the patient's genetic background exceedingly important in the etiology of chronic arthritis. Stress is laid upon various forms of treatment and the necessity for adjusting the therapeutic measures to the patient as well as to the known or surmised etiological factors. Margolis feels that available therapy is of great value even in advanced cases. Dietary, physiotherapy, and medicinal procedures are explained with conservative opinions as to probable results. This phase of the subject is developed very well, for although much information relative to treatment is given, there is nothing which would tend to induce or enable a patient to treat himself without the advice of his physician. Just as manuals on diabetes mellitus, on nutrition, and upon other subjects have served to bring the physician and his patient into a clearer understanding of their mutual problem, so this book should be of distinct value in the treatment of intelligent patients with chronic arthritis.

J.C.B.

College News Notes

Dedicatory exercises for the new Medical Laboratory Building of the University of Texas, the John Sealy Hospital Outpatient Building and the Rebecca Sealy Residence for Nurses were held at Galveston, May 30-31, 1932. Dr. George E. Bethel (Fellow), Galveston, delivered the address of welcome. Dr. M. L. Graves (Fellow), Emeritus Professor of Medicine of the University of Texas, presented two clinics, and Dr. L. F. Barker (Fellow), Emeritus Professor of Medicine at the Johns Hopkins University School of Medicine, gave a medical clinic.

Mrs. Helen Felch Jennings, wife of Dr. Charles Godwin Jennings (Master and Second Vice President of the College), died suddenly immediately following the San Francisco Clinical Session. Mrs. Jennings was a daughter of Alpheus Felch, Fourth Governor of Michigan, a descendant of one of the early settlers of that State.

Dr. Walter A. Bastedo (Fellow), New York, Dr. Oscar Bethea (Fellow), New Orleans, Dr. Charles L. Brown (Fellow), Ann Arbor, Dr. Henry Christian (Fellow), Boston, Dr. Bernard Fantus (Fellow), Chicago, and Dr. Virgil E. Simpson (Fellow), Louisville, attended a meeting at Philadelphia, April 30, as members of the Sub-Committee on Scope of the United States Pharmacopoeia Revision Committee. This Committee is now selecting the newer remedies for the Pharmacopoeia. Many of these are patented, and over such the Pharmacopoeia can exert no control. As their titles and descriptions are legalized, the Committee can make such a remedy official only if the patentee agrees to every word of the text used by the Pharmacopoeia and agrees to abide by the standard so set for his product. In many cases, this agreement is refused. In some cases where it is accepted, manufacturers of allied products claim an equal right to a place in the Pharmacopoeia, on the ground that pharmacopoeial recognition of only one member of a class would be unjust discrimination and would afford an unfair advertising opportunity.

Dr. F. M. Pottenger (Fellow and President of the College), Monrovia, Calif., gave an address at the annual meeting of the State Medical Association of Texas at Waco, Texas, May 7, 1932, on "The Relations of Tuberculosis to General Medicine".

The Central Tri-State Medical Society, composed of physicians of Kentucky, Ohio and West Virginia, recently conducted its annual meeting. The entire scientific program was offered by Fellows of the College, as follows:

Dr. Walter Freeman, Washington, D.C. —"Conservative Treatment of Head Injuries";

Dr. J. Shelton Horsley, Richmond, Va.—"Cancer of the Stomach";

Dr. Charles H. Cocke, Asheville, N. C. —"Certain Phases of the Healing Process of Tuberculosis".

Dr. Louis F. Bishop (Fellow) and Dr. Louis F. Bishop, Jr. (Fellow), both of New York City, took part in the scientific exhibit at the meeting of the American Medical Association, New Orleans, May 9-13. Their exhibit consisted of electrocardiograms with descriptive titles on Vertigo and Syncope in Cardiac Arrhythmias.

An examination of the Program of the annual meeting of the American Medical Association discloses that eighty-nine Fellows and four Associates had official assignments.

Dr. J. Burns Amberson, Jr. (Fellow), Assistant Professor of Clinical Medicine,

Columbia University College of Physicians and Surgeons, was the guest lecturer and delivered a didactic lecture each day, followed by bedside instruction, in connection with the Five-Day Postgraduate Tuberculosis Institute League at the Jersey City Medical Center, May 16-25, under the joint auspices of the Hudson County Medical Society, Hudson County Tuberculosis League and the Hudson County Tuberculosis Sanatorium and Clinics. Dr. Amberson's subjects were: Pathology and Pathogenesis.

Dr. Asher A. White, son of Dr. S. Marx White (Fellow and Ex-President of the College), has been awarded the Alexander Cochrane Bowen scholarship in medicine, and will spend next year with Dr. Francis R. Fraser. The scholarship affords opportunity for one year postgraduate study and research at St. Bartholomew's Hospital in London. Dr. White received his M.D. degree from the University of Minnesota in 1929. He was interne and then resident in the New York Hospital for two years with Dr. Lewis A. Conner (Fellow) and Dr. Nellis Foster.

Dr. William H. Walsh (Fellow), Chicago, has been selected as the Medical Consultant of a new Medical Center at Monterrey, Mexico, by the Governor and Secretary of the State of Nuevo Leon. The new Medical Center contemplates a new medical school, a general hospital of five hundred beds, a nurses' home, a separate wing for tuberculosis, one for the insane, and another for communicable diseases. Dr. Walsh was formerly Executive Secretary of the American Hospital Association, and is now engaged in hospital planning, organization, management and equipment.

Dr. Frederick J. Farnell (Fellow), Providence, R. I., Chairman of the Public Welfare Commission of the State of Rhode Island, is the author of the following articles which appeared recently in the United States Daily:

"Task of Reshaping Characters of Paroled Convicts";

"Conflict of Prison Industries with Products of Free Labor";

"Sanitation as Crime Preventive".

Dr. Frank Parsons Norbury (Fellow), Jacksonville, Ill., was initiated to honorary membership in the Illinois Epsilon Chapter of Phi Beta Kappa fraternity recently. Dr. Egerton L. Crispin (Fellow), Los Angeles, Calif., is a member of the Alumnus Membership Committee of this national honorary fraternity.

The obituary notice for Dr. John Alden Lichty which appeared in the July issue of the Annals was prepared by Dr. Clement R. Jones, Regent. Through oversight the usual acknowledgement was not made.

Dr. Wann Langston (Fellow), Oklahoma City, Okla., appeared on the circuit postgraduate course of the University of Oklahoma, Extension Department, June 13-15, lecturing on the subject "General Vascular Disease, Hypertension and Myocardial Disease" at Clinton, Elk City, Woodward and Alva, Okla.

Dr. J. W. Torbett (Fellow), Martin, Texas, addressed the North Texas Medical Association at its regular semi-annual session at Bonham, Texas, on June 15 on the subject: "The Intradermal Use of Bacterial Antigens for the Diagnosis and Treatment of Several Chronic Diseases". Dr. Torbett read a paper before the State Medical Association of Texas at its May meeting in Waco on the subject of "Peribronchial Glands as a Focus of Systemic Diseases".

Thurman Delna Kitchin (Fellow), Wake Forest, North Carolina, President of Wake Forest College, was recently appointed by Governor O. Max Gardner of North Carolina a Member of the Commission for the Improvement of Laws. In May of this year, Dr. Kitchin became a member of the Duke (Rho) Circle of Omicron Delta Kappa, and on June 8, 1932, the LL.D. degree was conferred upon him by Duke University.

Dr. Ray M. Balyeat (Fellow), Oklahoma City, addressed the Twin Lakes District Medical Society, Rockwell City Iowa, at its Tenth Annual Assembly, June 16, on the subject of "Diagnosis and Treatment of Allergic Diseases".

Acknowledgement is made of the following gifts to the College Library of publications by members:

Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;

Dr. Algernon B. Jackson (Fellow), Washington, D. C.—4 reprints;

Dr. H. R. Livengood (Fellow), Elizabeth, N. J.—1 reprint;

Dr. Robert U. Patterson (Fellow), Washington, D. C.—1 reprint;

Dr. Clair L. Stealy (Fellow), San Diego, Calif.—1 reprint;

Dr. Samuel Weiss (Fellow), New York, N. Y.—1 reprint.

Dr. Robert U. Patterson (Fellow), Surgeon General of the U. S. Army, was the recipient of the honorary degree of Doctor of Laws bestowed by his Alma Mater, McGill University, at the annual Convocation of that institution for the conferring of degrees on May 26, 1932.

Dr. Rock Sleyster (Fellow), Wauwatosa, Wis., was re-elected a member of the Board of Trustees of the American Medical Association for five years, during the New Orleans meeting, May 12.

Dr. C. W. Greene (Fellow), with Dr. Frank A. Hartman, Dr. J. J. Maisel and Dr. G. W. Thorn, all of the University of Buffalo, were awarded the gold medal by the Committee on Awards of the American Medical Association in connection with the scientific exhibit at the New Orleans Session, "for original investigative work on the development and use of a hormone from the suprarenal cortex and excellence of presentation".

Dr. J. Arnold Bargen (Fellow), Dr. P. W. Brown (Fellow), with Dr. H. M. Weber, of the Mayo Clinic and Foundation, Rochester, Minn., were awarded the bronze medal, "for original investigation of diseases of the colon and excellence of presentation".

Dr. Ross V. Patterson (Fellow), Dean of Jefferson Medical College of Philadelphia, was honored, June 13, by Colgate University with the degree of Doctor of Science.

Dr. Mary O'Malley (Fellow), Washington, D. C., was elected President-Elect of the Medical Women's National Association at the annual meeting of that Society in New Orleans, May 9.

Dr. Herbert L. Bryans (Fellow) Pensacola, Fla., was recently reappointed a member of the Committee on Publication of the Journal of the Florida Medical Association.

"A New Non-surgical Method of Treatment for Gastric and Duodenal Ulcer" was the subject of an address delivered by Dr. L. Winfield Kohn (Fellow), New York, before the New York State Medical Society's meeting at Buffalo, May 25, 1932.

Dr. Edward J. Engberg (Fellow), St. Paul, Minn., was re-elected Secretary of the Minnesota State Board of Medical Examiners for the term of one year, at the May meeting of the Board.

Dr. Ralph deBallard Clarke (Fellow), Meriden, Conn., presented a popular public lecture on May 4 on the subject of "What is New in Tuberculosis" to a group comprising parent-teachers' organizations, public health association members, classes from the Nursing School of the Meriden Hospital, and the general public. Compression therapy and collapse surgery were illustrated by X-ray films, as they were applicable to a series of tuberculous children and adolescents.

Dr. Joseph Rogers Darnall (Fellow), Major, Medical Corps, U. S. Army has been awarded the Order of the Purple Heart. Major Darnall was wounded in action during the Meuse-Argonne offensive, October 28, 1918. Major Darnall also received a departmental commendation for his foresight and work in preventing a possible epidemic during the emergency occasioned by water shortage in Zamboanga, P. I., while he was stationed there as Surgeon in 1928.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., read a paper entitled "Recent Ad-

vances in Treatment; Hemorrhagic Diseases, Anemias, Uremia and Dropsy, Muscular Dystrophies, Diphtheria, Chorea and Meningitis" before the Medical Society of New Jersey at its annual meeting in Atlantic City, June 16, 1932.

Dr. Elliott P. Joslin (Fellow), Boston, Mass., addressed the annual meeting of the Fifth Councillor District of the Medical Society of the State of Pennsylvania at York, July 28, on diabetes.

Dr. Ada E. Schweitzer (Fellow), Indianapolis, Director of Infant and Child Hygiene on the Indiana State Board of Health, conducted a Child Health Institute, Winona Lake Chautauqua, July 3 to 9, inclusive. The program was devoted to home protection and to the conservation of the child by the home in cooperation with the community and with organized lay groups and professional and official agencies.

Dr. Waller S. Leathers (Fellow), Nashville, Tenn., was re-elected President of the Nashville Board of Medical Examiners for the coming year, during their annual meeting at Washington, May 2.

Dr. Alvin G. Foord (Fellow), Pasadena, Calif., was made President-Elect of the American Society of Clinical Pathologists at its meeting in New Orleans, May 6-9.

Dr. William H. Robey (Fellow), Boston, Mass., was recently elected President of the Suffolk District Medical Society.

Dr. Henry F. Stoll (Fellow), Hartford, Conn., was elected President of the Hartford County Medical Association at its one hundred and fortieth annual meeting on April 5, 1932.

Dr. Cecil Lorio (Fellow), Baton Rouge, La., was made President of the Louisiana State Pediatric Society at its meeting in New Orleans, May 10.

THE 1932 GRADUATE FORTNIGHT OF THE NEW YORK ACADEMY OF MEDICINE

Tumors, benign and malignant, will be the theme of the 1932 Graduate Fortnight of the New York Academy of Medicine to be held Oct. 17-28. The medical profession of the country is invited to participate in the intensive two week study of this important medical and surgical subject. A full program of clinical demonstrations, lectures and conferences has been arranged to cover all phases of tumors, their diagnoses and treatment.

Concurrent with the Fortnight, and for an added week thereafter, there will be housed in the Academy building an exhibition of anatomical specimens numbering approximately 3000 units. A number of the sections in the exhibition will be subjected to lecture demonstrations at regular intervals.

Ten evening meetings have been arranged during which tumor growths in various parts of the human anatomy will be discussed. Among the speakers are included Doctors W. Gordon M. Byers, Edwin Beer, Charles A. Elsberg, James Ewing, Donald C. Balfour, Daniel F. Jones, Dean Lewis and Francis Carter Wood.

Thirty afternoon clinical meetings and demonstrations have been arranged in eighteen of New York City's leading hospitals, including Bellevue, Lenox Hill, Presbyterian, St. Luke's, Fifth Avenue, Post-Graduate, Neurological Institute and others.

There is no charge for attendance at any of the clinics or meetings, but registration is required for participation in the hospital demonstration clinics. A complete program and registration blank for the clinics and demonstrations may be secured by addressing The New York Academy of Medicine, 2 East 103rd Street, New York City.

OBITUARIES

DR. LEONARD F. C. WENDT

Dr. LEONARD F. C. WENDT (Fellow), Detroit, Michigan, died suddenly June 11, 1932, of heart disease at the age of 56 years.

Dr. Wendt was born in Detroit, the son of Henry R. and Julia Wendt. He graduated from Baldwin University, Berea, Ohio, in 1896, receiving the degree of Bachelor of Sciences, and from the Detroit Homeopathic College in 1902, receiving the degree of Doctor of Medicine. He received the honorary degree of Doctor of Science at Baldwin University in 1928.

Dr. Wendt was Chief of the Diabetic Clinic at Grace Hospital, Detroit, for fifteen years. He was also a member of the Executive Board of that hospital. During the World War he was Secretary of the local Medical Advisory Board, as well as its examiner. He was Grace Hospital's volunteer physician at Camp Custer. At one time he taught diagnosis and pediatrics at the old Detroit Homeopathic College, and during 1915 was Instructor in Physical Diagnosis in the Detroit College of Medicine and Surgery. He was Consulting Physician at Miriam Memorial Hospital and Attending Physician to the Eloise Hospital for Mental Diseases. Dr. Wendt was the author of several monographs on diabetes.

He will be remembered for many years to come for his work among diabetic children. In their interest, he established a summer camp on a lake near Brighton, Michigan, in 1926. He continued this project each year with the help of the Red Cross and of Grace Hospital, but at great expense to himself personally. Many children from Detroit and other parts of the State, who otherwise might have had to suffer their affliction in the heat of the city, have been greatly benefited. The camp will be continued and will be known as the Leonard Wendt Camp for Diabetic Children.

Dr. Wendt was a member of the Wayne County Medical Society, the Michigan State Medical Society, a Fellow of the American Medical Association, a member of the Interstate Medical Society, the Michigan Trudeau Society, the Society for the Advancement of Science, and the Association for Internal Secretions. He had been a Fellow of the American College of Physicians since 1920.

(Furnished by WILLIAM M. LEFEVRE, M.D., F.A.C.P., Muskegon, Michigan.)

DR. FREDERICK WILMOT MANN

Dr. FREDERICK WILMOT MANN (Fellow), Houlton, Maine, died June 16, 1932, at the Aroostook Hospital following an emergency operation for acute intestinal obstruction. Dr. Mann had seen his patients the day before, and had planned to leave for the annual meeting of the Maine Medical Association at Rangeley the very day on which his death so suddenly and unfortunately occurred.

Dr. Mann was born at Baillie, New Brunswick, Canada, May 18, 1868, the son of Thomas Andrew Mann and Sarah Ann Gilmore. He was a graduate of the College of Physicians and Surgeons of Baltimore in 1892, and of the University of Bishops College

Faculty of Medicine of Montreal in 1900, receiving the degrees of M.D. and M.D., C.M., respectively. He first practiced medicine in Monticello, Maine, and then removed to Houlton, where he had practiced for over thirty years. He did postgraduate work at the Boston University during 1919 and 1920. He was a member of the Visiting Staff of the Madigan Memorial Hospital and the Aroostook Hospital, and had acted as lecturer to student nurses at both institutions for several years. Dr. Mann was a charter member and ex-President of the Aroostook County Medical Society, a member and ex-President of the Maine Medical Association, a Fellow of the American Medical Association, a member of the British Medical Association, a member of the Council of Physicians and Surgeons of New Brunswick, Canada, and had been a Fellow of the American College of Physicians since April 8, 1929. In addition, Dr. Mann was a Director of the Aroostook Anti-Tuberculosis Association, a member of the Houlton School Board (serving his second term—its Chairman during 1931) and a member of many local organizations.

Dr. Mann was keenly interested in civic and educational affairs. He was an eager student of medicine; his counsel was often sought. His fund of amusing stories, his ability to quote poetry, his genial personality made him welcome in any group. Above all, he was one of the ablest internists of his state, and a brilliant physician.

DR. BYRON FULLER BARKER

Dr. Byron Fuller Barker (Fellow), Bath, Maine, died on April 29, 1932, from acute appendicitis. Dr. Barker was born in Bath, November 19, 1872. He received the degree of Bachelor of Arts from Bowdoin College in 1893, and the degree of Doctor of Medicine from the Jefferson Medical College in Philadelphia in 1896. He was a member of the Medical Staff of the Bath City Hospital, and taught a course in Internal Medicine to the Nurses of that institution.

Dr. Barker was an ex-President of the Sagadahoc County Medical Society, ex-Secretary of the Bath Medical Club, a member of the Maine Medical Association, the American Medical Association, and had been a Fellow of the American College of Physicians since 1931.

Quoting from the Maine Medical Journal, "His life was devoted to the practice of medicine; he read widely, had few if any, side issues, took short and few vacations and was a model of what a careful, cheerful, conscientious medical advisor should be. He studied the latest medical treatises and had them ready in mind for emergencies. He was keen in diagnosis, was trusted implicitly, and was a pleasing gentleman in the house of sickness".

(Furnished by E. W. Gehring, M.D., F.A.C.P., Governor for Maine.)

DR. BENJAMIN FRANKLIN SHUTTLEWORTH

Dr. Benjamin Franklin Shuttleworth (Fellow), died at his home in Clarksburg, W. Va., March 31, 1932, from cardiac failure; aged 54 years. Dr. Shuttleworth was one of the most prominent physicians of the State. He received his Bachelor of

Arts degree at the West Virginia University before entering Jefferson Medical College of Philadelphia, from which he was graduated in 1905. Since graduation, he practiced in Clarksburg, where he was universally esteemed by the profession. Dr. Shuttleworth was honored by being appointed to the West Virginia State Council of Health. He belonged to the Harrison County Medical Society, and was an ex-President of the West Virginia State Medical Association. He was a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1922. His wife, surviving him, was Miss Rachael Farris.

(Furnished by JOHN N. SIMPSON, M.D., F.A.C.P., Governor for West Virginia.)

The September Number of the Annals of Internal Medicine

Clinical Aspects of Gastric Secretion ..... ARTHUR L. BLOOMFIELD

Standards of Normal in Gastric Secretion ..... WALTER C. ALVAREZ

Asthma: Clinical Types and Principles of Therapy ..... EDWARD L. BORTZ and GEORGE MORRIS PIERSOL

The Clinical Study of the Atrophic Tongue ..... WILLIAM S. MIDDLETON

The Significance of Fever in Regard to Defense Against Infection.... HOBART A. REIMANN

Poisonous Spider Bites ..... EMIL BOGEN

Studies on a Urinary Proteose. II. Skin Reactions and Therapeutic Applications in Hay Fever ..... WARD DARLEY and RICHARD W. WHITEHEAD

The Successful Treatment of Hay Fever and Pollen Asthma ..... ALEXANDER STERLING

Cardiac Failure. Report of a Case of Cardiac Decompensation of Fourteen Months Duration ..... EDWARD J. STIEGLITZ

Generalized Myositis Fibrosa.. EDWARD H. SCHWAB, PAUL BRINDLEY, and MEYER BODANSKY

Roentgenologic Diagnosis of Early Pulmonary Tuberculosis ..... B. R. KIRKLIN

Medical Humorists: Medical Men as Inventors: Medical Men as Explorers ..... ERNEST WEINFIELD